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A.M.A. ARCHIVES OF

INTERNAL MEDICINE

The Clinical Implications of Antidiuretic Hormone Activity
Abraham G. White

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W. R. O. Goslings and K. Büchli

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Hodgkin's Disease and Pregnancy
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The Oxidative Activity of Blood Serum in Schizophrenic and Manic-Depressive Psychoses
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Cryptococcal Meningitis Treated with Amphotericin B
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Anxiety as a Manifestation of Pheochromocytoma
Brewster C. Doust

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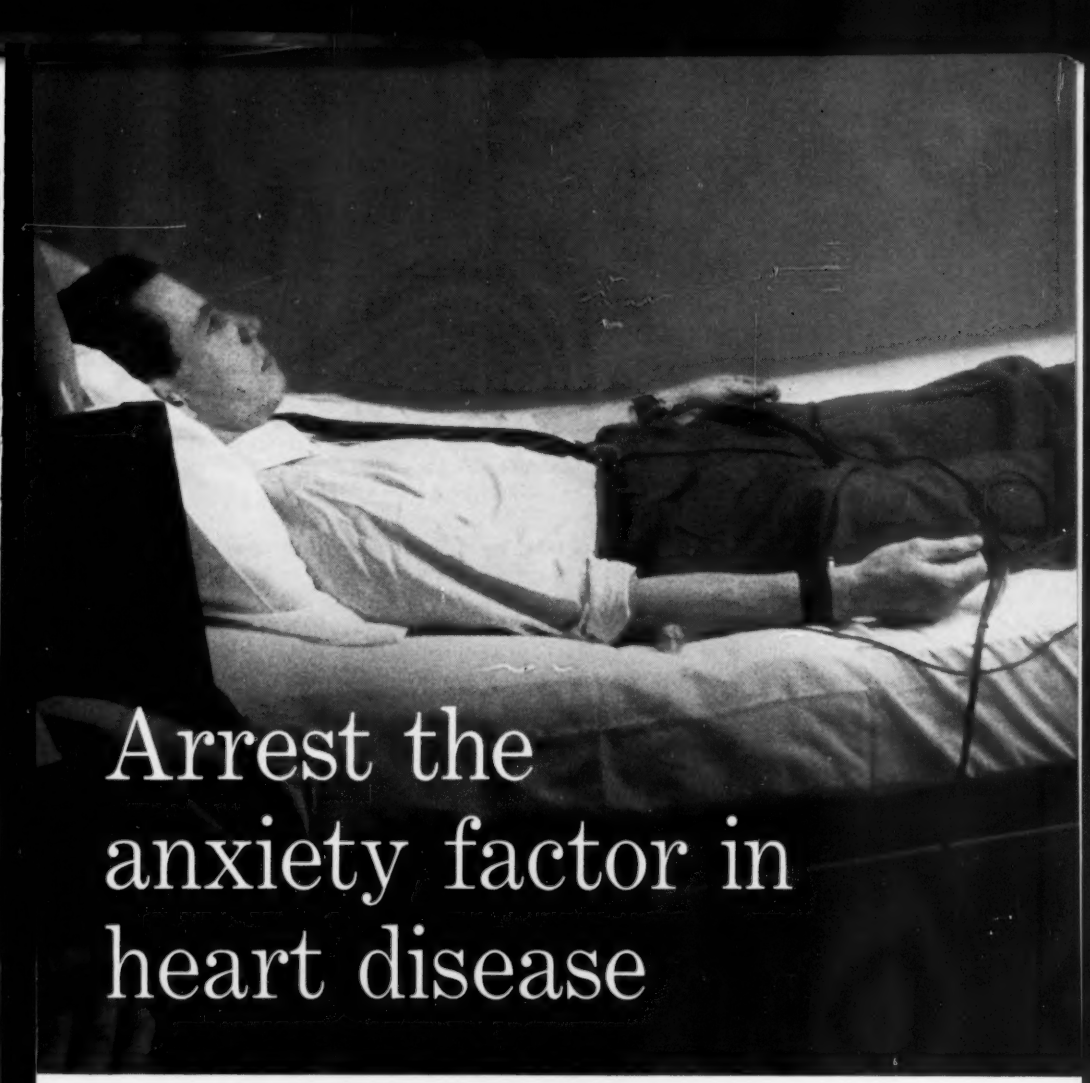

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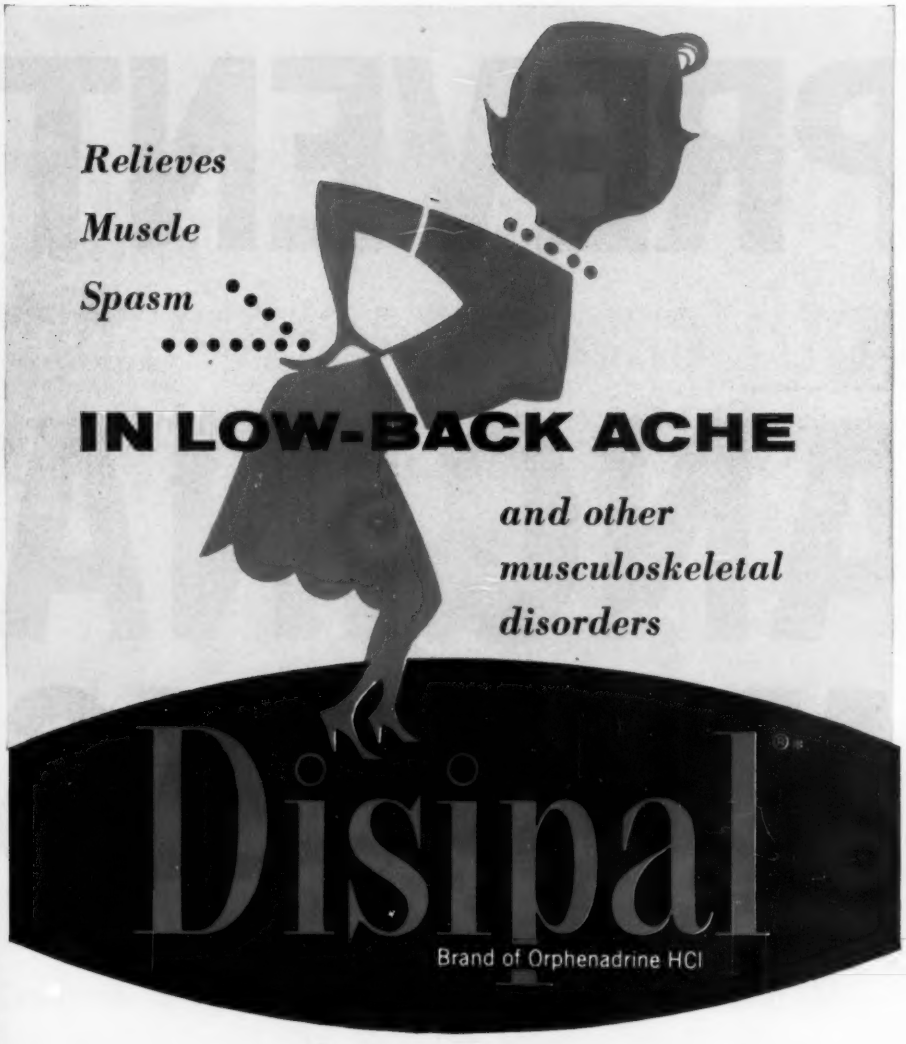

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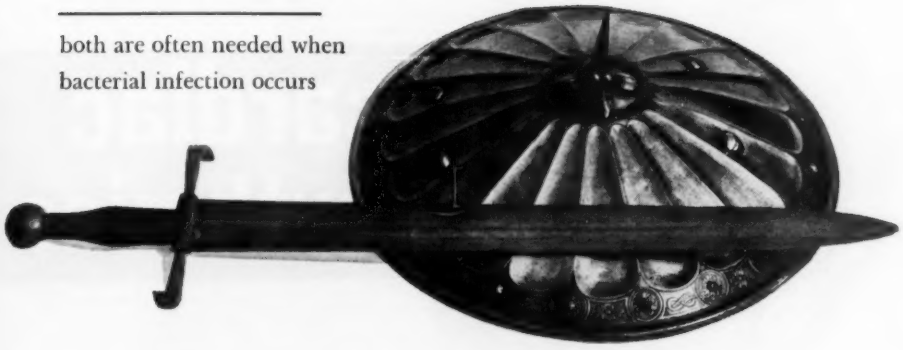

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Editorials

The Clinical Implications of Antidiuretic Hormone Activity

Perspectives and Dilemmas

Devotees of Bacchus notwithstanding, water has been a major determinant of the life and death of men and civilizations. That it also is the anlage of our earliest phylogenetic and ontogenetic habitat has probably contributed to the intense interest in, and study of, the metabolism of this ubiguitous compound. Since body water is of such importance to the survival of the organism, one anticipates, at least on teleological grounds, the existence of homeostatic mechanisms for the maintenance of its integrity. The purpose of this paper is to review briefly current information and concepts about these mechanisms, including the neurohypophyseal antidiuretic hormone (ADH) and other possible antidiuretic mechanisms, with special reference to their role in disturbances of water metabolism.

In particular, one question concerns us: Does increased ADH activity play an important causative role in water-retaining states like hepatic cirrhosis, congestive heart failure, and the nephrotic syndrome? The relevant experimental data may be grouped as follows:

1. Evidence pertaining to the role of the neurohypophyseal ADH in water-retaining states.
2. Evidence that increased ADH activity may not play a role in water-retaining states.
3. Further evidence for extrahypophyseal antidiuretic mechanisms.

1. Evidence Pertaining to the Role of Neurohypophyseal ADH in Water-Retaining States

Of the approximately 120 ml. of water filtered each minute through the glomeruli of the normal subject, about 85% presumably undergoes tubular reabsorption isoosmotically along with reabsorbed solute. The reabsorption of the remaining 15% appears to be under the control of ADH, and it is by means of this mechanism that the integrity of body water is ordinarily maintained.[1] Under the circumstances of *normal* renal hemodynamics, solute ingestion and excretion, and endocrine balance, antidiuresis reflects increased ADH activity, and it is the extension of this theorem, without reservation, to the patient suffering from the retention of water that underlies much of the evidence to be presented for the role of ADH in water-retaining states. The limitations of this assumption will become apparent later.

Thus, the occurrence of impaired water diuresis in patients suffering from hepatic cirrhosis [2] or from congestive heart failure [3] has suggested increased ADH

Submitted for publication July 15, 1958.

Department of Medicine, The Mount Sinai Hospital.

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activity. Furthermore, metabolic balance studies on patients recovering from congestive heart failure [4] as well as on those undergoing further cardiac decompensation [3] have indicated, in some instances, a retention of water out of proportion to that of sodium, again raising the possibility of increased ADH activity. A similar primary (i. e., not secondary to that of sodium) retention of water with resulting hyponatremia has been observed following the prolonged administration of vasopressin (Pitressin) tannate in oil to both normal subjects [5] and those suffering from congestive heart failure [3] or hepatic cirrhosis.[6] While this regimen tends to cause urinary loss of sodium in control subjects, it may not do so in some of the cardiac or hepatic patients.

Finally, increased ADH activity as a primary causative mechanism underlying the retention of water has been implicated by the demonstrations of increased concentrations of an antidiuretic substance (ADS) in the urine of patients suffering from toxemia of pregnancy,[7] hepatic cirrhosis,[2,8] the nephrotic syndrome,[9] and congestive heart failure [10]; also, by the reports of increased concentrations of ADS in the serum of some such patients.[11]

2. Evidence That Increased ADH Activity May Not Play a Role in Water-Retaining States

Among the types of studies suggesting that increased ADH activity may not actually play a role in water-retaining states are those purporting to show no increase of an antidiuretic substance in either the sera or urines of such patients.[12] Such differences in experimental results are related to variations in the type of bioassay used in these determinations, including the method of preparing the test substances (serum, urine) for assay as well as the species of test animals, the physiological state of the test animal (e. g., hydration, anesthesia), and the route of administration of the test material.

Since differences in the type of bioassy yield such varibale interpretations concerning the concentrations of ADS in the sera and urines of patients suffering from the retention of water, the proposal has been made that ADS may not be derived from, or reflect, ADH secretion and activity. This matter has recently been reviewed extensively,[13] and it seems fair to conclude, tentatively, that ADS may not represent ADH at all.

Assuming, for the moment, that this increase in serum and urinary ADS does represent increased secretion and activity of ADH, it could result from increased secretion and/or decreased inactivation of ADH. Thus, since the liver is one of the principal sites of inactivation of ADH, it was tempting to postulate that the damaged liver in hepatic cirrhosis cannot inactivate ADH normally, thus leading to increased ADH activity and resultant retention of water.[2]

The development of a reproducible human bioassy of vasopressin [14] made it possible to test the hypothesis of decreased inactivation of ADH in hepatic cirrhosis and later in congestive heart failure.[15] Physiological doses of vasopressin were inactivated normally and, assuming that vasopressin is handled similarly to ADH, it was concluded that there is, in fact, no impaired inactivation of ADH in these disease states. Experiments employing the parenteral administration of nicotine salicylate to patients suffering from hepatic cirrhosis [16] or from congestive heart failure [3] indicate that vasopressin is indeed handled similarly to ADH. Thus, nicotine, which stimulates the release of endogenous ADH, caused essentially normal antidiuresis in these patients. A suggestive trend toward

abnormal accumulation of edema following prolonged administration of vasopressin tannate in oil to cirrhotics has been reported,[6] with the implication that although such patients can handle physiological doses of the hormone, they are incapable of inactivating large amounts.

Patients suffering from hepatic cirrhosis or congestive heart failure attained peak diuresis, during intravenous hydration with 5% dextrose in water, in the same time as normal subjects, although the magnitude of the peak diuresis in the cardiac patients was subnormal.[14,15] Since the time required to attain peak diuresis is believed to be a measure of circulating ADH,[17] this finding implied that there may be no overproduction of ADH in these disease states and/or that the increased antidiuretic material in the serum and urine of such patients (if ADS really exists) may be of extrahypophyseal origin.

In fact, the only metabolic abnormality resulting from the intravenous injection of vasopressin was a decrease in serum sodium of patients with hepatic cirrhosis which was ascribed to a shift of sodium into cells[14]; similar results have been obtained with the administration of vasopressin tannate for longer periods to such patients.[6]

These indirect methods of showing that there may be no increased ADH activity in hepatic cirrhosis or congestive heart failure were supported subsequently by experiments employing the administration of ethyl alcohol to such patients.[18] In these studies alcohol produced little or no diuresis of water, and since alcohol is presumed to inhibit the secretion of ADH,[19,20] such a finding suggested that ADH secretion is at a minimum in these disease states. However, it has recently been postulated that ethyl alcohol may be only a relative inhibitor of ADH secretion,[21] because, in above-threshold doses, nicotine may produce antidiuresis in a subject previously given alcohol. Since no details are given concerning the physiological effects of such doses of nicotine in these subjects, e. g., on renal hemodynamics, this question had best be considered unanswered at this time.

The secretion of ADH is inhibited in the normal subject by decreased plasma tonicity[22] and probably by increased volume of the extracellular compartment, or some function thereof.[23] Both these conditions may be observed in patients suffering from water-retaining states like hepatic cirrhosis, congestive heart failure, and the nephrotic syndrome. To reconcile this paradox of apparent ADH overactivity in the presence of physiological factors normally inhibiting the secretion of ADH, there have been proposed what might be termed highly speculative explanations, such as "resetting of the osmotat" or peculiar sequestration of excess extracellular fluid.[24] What appears to be a more logical explanation of this apparent paradox is that there actually may be no overactivity of the neurohypophyseal ADH and that other antidiuretic mechanisms, discussed later, are probably responsible for the retention of water.

3. Further Evidence for Extrahypophyseal Antidiuretic Mechanisms

There are several observations which indicate the existence of extrahypophyseal antidiuretic mechanisms. Thus, water diuresis may be subnormal following th oral[25] or intravenous[26] hydration of patients with diabetes insipidus. Furthermore, in such patients the 24-hour urinary volumes never approach the 15% of the filtered water load[26,27] that would be expected in the absence of ADH.

Finally, massive edema has been observed in a patient with diabetes insipidus,[28] suggesting that ADH need not be a necessary factor in the accumulation of edema. More recently this observation has been confirmed by the experimental production of ascites in dogs suffering from diabetes insipidus.[29] Also, the presence of extrahypophyseal antidiuretic mechanisms may be inferred from the subnormal water diuresis observed in Addison's disease[30] and corrected by the administration of cortisone.

What is the nature of these possible extrahypophyseal antidiuretic mechanisms? These include alterations in (*a*) renal hemodynamics and (*b*) solute excretion. Thus, studies during a state of sustained water diuresis ("physiological diabetes insipidus") in 29 experiments in 17 normal semirecumbent human subjects[31] showed that glomerular filtration rate was directly correlated with maximal urinary flow and free water clearance and inversely correlated with the minimal urinary osmolar concentration during water diuresis. The rate of solute excretion was directly correlated with both the maximal urinary flow and minimal urinary osmolarity.

Corroboration of these results has come from the unilateral reduction of glomerular filtration rate (by compression of the renal artery) in water-loaded dogs,[32] leading to the production of urine hypertonic to plasma while the control kidney excretes water at a maximal rate; the effect of such reduction in rate of glomerular filtration has been ascribed to a reduction in the filtered load of sodium and chloride.

Pertinent to these experiments is the clinical fact that in the water-retaining states discussed in this review, as well as in Addison's disease, diminished glomerular filration rates, and excretion of solute (particularly sodium) tend to occur and may therefore serve as antidiuretic mechanisms.

Aldosterone, by reducing the excretion of sodium, tends to cause the retention of water and edema. Thus, increased amounts of aldosterone have been described in the urine in water-retaining states[33] during periods of low urinary excretion of sodium and positive water balance, suggesting that aldosterone may be a contributory extrahypophyseal antidiuretic mechanism. These views must be modified somewhat by the findings that (*a*) dietary restrictions of sodium, a regimen commonly employed in these patients, tends to produce an increase in urinary aldosterone, and (*b*) patients suffering from primary aldosteronism may show no edema.[34]

State of End-Organ Reactivity in Relation to ADH Activity

Since ADH promotes the reabsorption of water at some locus in the tubule, the activity of this hormone is reduced by inability of the tubular cells to react to it as a result of either metabolic or morphologic abnormality. Thus metabolic abnormality of the tubular cells may lead to nephrogenic diabetes insipidus,[35] in which there is an apparently inborn defect of renal tubular metabolism characterized by diminished reabsorption of water in the distal segment of the nephron, which is unresponsive to extracts of the posterior lobe of the pituitary.

Renal disease, if severe, may lead to what has been termed "end-organ diabetes insipidus,"[26,36] in which the per cent of the filtered water load excreted in the urine may exceed that observed in true (or "central") diabetes insipidus resulting from deficiency of ADH; "water-losing nephritis" is another term proposed for this condition.[37] In fact, the urinary excretion of water and total solute may exceed 40% of the filtered load as a result of tubular damage leading to

inability to reabsorb water and solute normally [26,36]; this high excretion of solute may contribute to the diminished reactivity of the tubule to ADH.

Overreactivity of the tubular cells to ADH does not appear to have been reported as yet.

Summary

Evidence is presented both for and against a major causative role of the neurohypophyseal antidiuretic hormone (ADH) in water-retaining states. It is suggested that, on balance, the evidence *against* such a role for ADH is preponderant. Attention has been drawn to the possible participation of extrahypophyseal antidiuretic mechanisms, including diminished glomerular filtrations rate and solute excretion, as well as increased secretion of aldosterone. Also, the existence of extrahypophyseal antidiuretic secretions (other than ADH) cannot be excluded. The one certainty about these water-retaining states is that in the overwhelming proportion of such patients the retention of water is associated with that of sodium and that where sodium is not excessively retained, neither is water.

Finally, mention has been made of the fact that diminished reactivity of the end-organ, the renal tubule, to ADH may cause abnormalities of water metabolism which simulate diabetes insipidus in some respects, in that the per cent of filtered water excreted in the urine is abnormally high.

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A.M.A. ARCHIVES OF
INTERNAL MEDICINE

Nasal Carrier Rate of Antibiotic-Resistant Staphylococci

Influence of Hospitalization on Carrier Rate in Patients, and Their Household Contacts

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Introduction

It is a generally accepted fact today that the increase in the percentage of infections in hospitals caused by antibiotic-resistant staphylococci is largely due to cross infection in the hospitals with resistant micro-organisms.[1-17] It is also known that among hospital staff, nurses, and patients the percentage of carriers of pathogenic staphylococci in the pharynx and vestibulum nasi and the percentage of resistant strains in these carriers are increasing in relation to the period of their stay in hospital. However, there is only a little information in regard to the period that patients continue to carry the resistant staphylococci acquired in the hospital after discharge and how far transfer of these micro-organisms to household contacts occurs. Dowling et al.[18] found in Chicago that the carrier rate for staphylococci in the nose and/or throat of patients, counting all staphylococci irrespective of their ability to produce pigment or hemolysis and of their coagulase activity, decreased from 74% at the time of discharge to 31% four weeks after discharge. After this the percentage remained between 31% and 39% in the following weeks, with a maximal observation period of 7 to 21 weeks. The percentage of penicillin resistant strains in these carriers decreased regularly. The decrease in rate for all types of staphylococci, together with the decrease in the percentage of resistant strains in these carriers, caused a gradual fall in carrier rate of resistant staphylococci from about 65% (88% of 74% carriers) at the time of discharge to only about 12%-16% (about 40% of 30%-40% carriers) six to eight weeks after discharge. A similar course could be observed for the resistance to chlortetracycline. At the time of discharge 78% of the strains required 10 μg. of chlortetracycline per milliliter or more for inhibition. After 6 weeks this figure was 33, and in the period of 7 to 21 weeks the average of the resistant strains was 14%. The investigators regarded these figures as normal for a population which has not been in contact with the hospital, as they found about the same percentages in the household contacts of these patients. They could further demonstrate that transfer of resistant staphylococci of discharged patients to household

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This investigation was supported by a grant from the National Health Research Council T. N. O., Holland. The Royal Netherlands Fermentation Industries Ltd., Antibiotic Div., Delft, gave financial help also. More than 50 general practioners in and around Leyden took the nasal swabs from discharged patients and their household contacts. Ir. W. A. Koek, statistician of the Royal Netherlands Fermentation Industries, Ltd., made the statistical analysis of our data.

contacts did occur but not frequently (7 instances in 209 household contacts of 54 families). Furthermore, a significant increase in the carrier rate of resistant strains among these household contacts was not observed during the entire observation period. These authors came to the conclusion that the hazard of the introduction of a single person carrying a resistant hospital strain was less than the number of other contacts in the general population who were carrying organisms of similar resistance.

A rate of 12%-16% carriers of penicillin-resistant staphylococci in a normal population is, however, higher than the 2%-4% cited in reports from various sources originally.[2,7,14] Reports from some countries of a more recent date,[19-21] however, do state higher rates, which are more in accordance to the figures found by Dowling et al. It seemed possible that, in spite of the fact that discharged patients show a considerable loss of resistant strains acquired in the hospital, a gradual infiltration of these strains had occurred in the population of Chicago in the preceding years, as a result of which a stabilization of the resistance rate at a higher level had taken place. Therefore it seemed useful to repeat this investigation in a country like the Netherlands, where according to available figures from preceding years the carrier rate of resistant staphylococci had remained limited to about 4%.[16,17] Furthermore, we have tried to examine whether and to what degree any correlation could be found between the antibiotic therapy which the patient had received during his stay in hospital and the type of resistance of the strain harbored by the patient after discharge. Such a knowledge could be of clinical interest in case a staphylococcal infection requiring antibiotic therapy should occur in such a patient at home after discharge (for example, staphylococcal pneumonia complicating influenza, staphylococcal septicemia, carbuncle).

Method of Investigation

On the first day of each week between Jan. 1, 1955, and Dec. 31, 1955, cultures from the vestibulum nasi were taken from all patients of the Department of Surgery, University Hospital of Leyden, whose discharge in that week was already settled beforehand. As the discharge of the patients was arranged independently of this investigation, it can be assumed that the material obtained in this way may be considered representative for all patients discharged from the Department of Surgery during that year.

The culture was made by swabbing both sides of the vestibulum nasi with a sterile cotton applicator dipped in sterile broth previously. The applicators were streaked across sheep-blood agar—one plate without penicillin, one plate with 1 unit of penicillin per milliliter. In general only a single colony with the appearance of a pathogenic Staphylococcus (pale yellow to golden-colored with hemolysis) was picked from each plate for further study. When the appearance of the colonies gave rise to the supposition that more types of staphylococci were possibly present, two or more colonies were picked. In those cases in which no resistant staphylococci were present, of course no staphylococci were found on the blood-agar plate containing penicillin. On the other hand, we succeeded several times in culturing some resistant Staphylococcus colonies on the penicillin-containing plate (which has a strong inhibitive effect on the whole flora of the nose) when they were overgrown by other bacteria than staphylococci on the plate not containing penicillin. Furthermore, it was sometimes possible to culture a resistant strain present in only small numbers, which were lost between large numbers of sensitive colonies of staphylococci on the plate not containing penicillin. Altogether, we succeeded in culturing 15% more resistant staphylococci with the culture on these two plates together than on blood agar not containing penicillin.

From the pure culture obtained coagulase activity was determined with the slide test (Cadness-Graves et al.[22]), as well as in a liquid medium with human plasma (Fisk[23]). Only coagulase-positive strains were counted as potentially pathogenic strains; all others, irrespective of their ability or inability to produce pigment or hemolysis, were counted as nonpathogenic. Pathogenic strains were further investigated regarding their sensitivity to penicillin, streptomycin, chlortetracycline, oxytetracycline, chloramphenicol, and erythromycin. All pathogenic strains were also phage-typed.

The sensitivity test was performed as a preliminary measure by means of filter-paper disks, according to the method described by Hoette and

Struyk.[24] Later, after collection of the entire material, the sensitivity of all strains was determined accurately according to the plate-dilution method in the way already described in a previous paper.[8]

As in the previous paper, the strains were divided into "sensitive" and "resistant" only. As "sensitive" were recorded those strains which showed a sensitivity for penicillin, streptomycin, chlortetracycline, oxytetracycline, and erythromycin of up to and including five times the sensitivity of the Staphylococcus Oxford-Heatly strain, cultured on the same test plates. For chloramphenicol, the line between sensitive and resistant was drawn at more than three times the sensitivity of the Oxford-Heatly strain.

These values are in accordance with the maximal ranges of sensitivity found in staphylococci cultured from patients who never received antibiotic therapy. This means that we report as resistant those strains which required for inhibition more than 0.1 unit of penicillin per milliliter (penicillinase-producing strains), more than 15μg. of streptomycin per milliliter, more than 5μg. of oxytetracycline per milliliter, more than 2.5μg. of chlortetracyline per milliliter, more than 15μg. of chloramphenicol per milliliter, and more than 2.5μg. of erythromycin per milliliter. It should be recorded that only few strains had values in the intermediate range of sensitivity but that the sensitivity of most of the strains was clearly under or very much above the values mentioned. Resistance to antibiotics other than penicillin in our material occurred only among strains which were also penicillin-resistant.

Phage typing was performed according to the directives given by Williams and Rippon.[25] The following set of phages was used*:

Group I —29, 52, 52A, 79
Group II —3A, 3B, 3C, 55, 71
Group III—6, 7, 42E, 47, 53, 54, 70, 73, 75, 77
Group IV—42D

Besides the phages mentioned, we also used a Bacteriophage 44B, adapted by ourselves from Phage 44, which was of some interest for the typing of our hospital strains, and a Bacteriophage No. adapted from the Bacteriophage 42E, which afterward appeared to be almost but not entirely identical with Bacteriophage 80, likewise adapted from Bacteriophage 42E by Rountree and Freeman.[26]

After the patient was discharged, a swab from the vestibulum nasi was taken, if possible, every two weeks for a period of six months to one year by the family doctor of those patients living in Leyden or its neighborhood and sent to us for culturing.

As a part of the patients had their work outdoors, this was not always possible. Besides, several patients withdrew themselves from the investigation in the long run. Furthermore, we discharged from follow-up those patients in whom three consecutive cultures no longer showed the original strain, either because it had been replaced by another strain or because the patient no longer harbored any pathogenic staphylococci in the nose at all. In the further course of the investigation we considered these patients as having definitely lost the original strain. If no culture was made in an intervening period but if the cultures before and after this period showed the same strain judged by pattern of resistance and phage type, the strain was assumed to have been present during the entire period. If the strains differed, however, before and after the failing date of culture, the patient was excluded for the relative point of time.

In addition to the follow-up of the patients themselves, cultures were also made every two weeks from the noses of those persons living in the same house, with whom the discharged patient came into contact regularly. The pathogenic Staphylococcus strains cultured from these household contacts were also examined for their pattern of resistance and phage type.

Results

1. *Percentage of Carriers in Patients at Moment of Discharge; Antibiotic Resistance and Distribution of Phage Groups in Strains Cultured.*—A nose swab could be cultured from 587 patients at the moment of discharge. In 337 patients, i. e., 57%, this culture yielded a potentially pathogenic

TABLE 1.—*Resistance to Six Antibiotics of Pathogenic Staphylococci Isolated from the Vestibulum Nasi of Patients at Moment of Discharge* *

Resistant to	No.	% of Total No. of Patients	% of Total No. of Carriers
Penicillin	224	38.2	66.5
Streptomycin †	174	29.6	51.6
Chlortetracycline & oxytetracycline †	124	21.1	36.8
Chloramphenicol †	50	8.5	14.8
Erythromycin †	13	2.2	3.9

* Number of patients examined, 587; number of carriers 337.
† Resistance to antibiotics other than penicillin occurred only in strains which were penicillin-resistant too.

* The bacteriophages were supplied by Dr. A. C. Ruys, Professor of Bacteriology at the University of Amsterdam, who also gave us the opportunity to study the technique of phage typing in her laboratory.

TABLE 2.—*Carrier Rate of Pathogenic Staphylococci and Resistance Rate in Carriers in Discharged Patients, Divided According to Month of Discharge*

Month	No. Examined	Positive Carriers	% of No. Examined	No. Resistant	% of No. Examined
January	39	22	56	13	33
February	64	40	63	29	45
March	46	27	59	18	39
April	44	30	68	21	48
May	35	17	49	12	34
June	52	27	52	19	37
July	46	27	59	19	41
August	41	24	59	15	37
September	38	22	58	16	42
October	71	40	56	25	35
November	63	37	59	22	35
December	48	24	50	15	31

Staphylococcus aureus. The resistance rate of these 337 strains against penicillin, streptomycin, chlortetracycline, oxytetracycline, chloramphenicol, and erythromycin has been summarized in Table 1.

In connection with the data of Gould and Allan,[27] who found that the carrier rate and the number of cross infections were less in the summer months, we divided our material also according to the month of discharge.

It can be seen from Table 2 that there was no seasonal influence either on carrier rate or on the percentage of resistant strains in our material.

The distribution of the cultures over the various phage groups is shown in Table 3.

The penicillin-sensitive strains, as far as typable, were rather equally divided over phage Groups I, II, and III. In the penicillin-resistant strains, there was as usual a preponderance of Group III strains. Of the Group III strains, 45% had the phage Type 53/75/77/−. Another 7% had phage Type 75/77/+. According to the rules laid down by Williams and Rippon,[25] one could count these as identical or at least as closely related to the former. Beside these phage types, another 18% of the Group III strains were characterized by a rather extensive but still well recognizable and specific phage pattern of 6/7/47/53/54/75/77/+. Strains of phage Type 44B were present in a definitely lower percentage than in 1953 in the same hospital (6.7% against 43.5% in 1953). As in 1953, resistant strains belonging to phage Group II were absent.

Both the carrier rate of pathogenic staphylococci and the percentage of resistant strains in the carriers increased clearly with the duration of stay in hospital (Table 4).

2. *Therapy and Pattern of Resistance.*—If we correlated every facet of the pattern of resistance of the strains separately with the fact of whether the patients had received antibiotic therapy homologous to the facet under consideration (for example, penicillin therapy in case of penicillin resistance, chloramphenicol therapy in strains with chloramphenicol resistance), we obtained the results shown in Table 5.

From these data it appears that all along the line the resistant strains occurred more frequently in patients who had received a homologous therapy. Nevertheless, this resistance-promoting influence of therapy should be considered to be of an indirect nature, not of a causative one. Among other things this appears clearly from the fact that all our penicillin-resistant strains produced penicillinase. The well-known fact that staphylococcal strains can be made re-

TABLE 3.—*Distribution of Phage Groups in Pathogenic Staphylococci Isolated from Vestibulum Nasi of Patients at Moment of Discharge*

	Total	Group I		Group II		Group III		Type 44B		Type No		Nonspecific		Nontypable	
	No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Penicillin-sensitive	113	19	16.8	18	15.9	22	19.5	0	0	6	5.3	6	5.3	42	37.2
Penicillin-resistant	224	14	6.2	0	0	164	73.2	15	6.7	21	9.4	3	1.3	7	3.1

TABLE 4.—*Carrier Rate of Staphylococci in Vestibulum Nasi in a Normal Population and in Discharged Patients in Regard to Duration of Hospitalization*

	Normal Population *		Discharged Patients Length of Stay in Hospital							
			0-7 Days		7-14 Days		2-4 Wk.		Longer	
	No.	% of Total	No.	% of Total	No.	% of Total	No.	% of Total	No.	% of Total
Total examined	370		212		178		124		73	
Carriers of S. aureus	128	35	109	51	90	50	87	70	51	70
S. aureus-sensitive	117	32	66	31	20	11	17	14	10	14
S. aureus-resistant	11	3	43	20	70	39	70	56	41	56
S. albus or no S.	242	65	103	49	88	50	37	30	22	30

* "Normal population" were the family members of the discharged patients.

sistant to penicillin through passage on penicillin-containing culture media in vitro is generally considered to have little or no clinical value, as the resistance thus obtained is not due to the production of penicillinase. Szybalski [28] and Lankford [29] observed that penicillin-sensitive strains not producing penicillinase may contain some penicillinase-producing mutants. Gould [30] also reported the genesis of penicillinase-producing variant from penicillin-sensitive cultures. In his case all these mutants did belong to phage Group III, even if the parent strain belonged to phage Group I or II. This would explain the preponderance of Group III in the resistant strains in the hospitals. It seems unlikely, however, that such a phenomenon could be responsible for the penicillin resistance in our material. About half of the penicillin-resistant strains of Group III did belong to one phage type; about 70%, to two phage types only. Such a unilateral-focused mutation in so many different patients seems incredible. The same holds true for the streptomycin-, chloramphenicol-, chlortetracycline-, and oxytetracycline-resistant strains; from the last-named strains 60% belonged to one phage type (53/75/77/−). Furthermore, nearly all the chlortetracycline- and oxytetracycline-resistant strains were cultured from patients who never had received therapy with these antibiotics. In the latter it was therefore very clear that the resistance was not induced by homologous antibiotic treatment but that the greater part of these strains had been acquired without homologous therapy.

The correlation between therapy and pattern of resistance becomes still less pronounced if the entire pattern and not only one facet of it is compared with the treatment received. If, e. g., a strain is resistant to penicillin, streptomycin, and chloramphenicol and the patient has received penicillin only, neither the streptomycin resistance nor the chloramphenicol resistance can be explained by the therapy. In our ma-

TABLE 5.—*Correlation of Therapy and Antibiotic Resistance of Pathogenic Staphylococci Isolated from Vestibulum Nasi of Hospitalized Patients at Moment of Discharge*

	Penicillin		Streptomycin		Chloramphenicol		Chlortetracycline & Oxytetracycline	
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant
No. of strains	113	224	163	174	287	50	213	124
Homologous therapy	27	160	13	77	11	16	2	5
% of homologous therapy	24%	71%	8%	44%	4%	32%	1%	4%

terial there was a total agreement between therapy received and the pattern of resistance in only 16% of all the resistant strains together, and this was mostly in strains resistant to penicillin or penicillin and streptomycin only, not in multiple-resistant strains. Of the strains showing streptomycin resistance besides resistance to other antibiotics, only 10% showed agreement. In the chloramphenicol-resistant strains which were all resistant to penicillin and mostly also to streptomycin, sometimes to chlortetracycline and oxytetracycline, there was agreement in only 2% of the strains. Of the strains resistant to chlortetracycline and oxytetracycline, the greater part of which were also resistant to penicillin, streptomycin, and chloramphenicol, there was no strain at all in which the total pattern of resistance was in accordance with the therapy received.

From this disagreement between antibiotic therapy and total pattern of resistance it stands out clearly that in general the resistant strains are acquired by the patients and do not emerge in them. This does not exclude the finding that in some cases antibiotic therapy in a patient may add a special facet in the already existing pattern of resistance of the strain acquired by that patient.

The above-mentioned data may be summarized as follows. Antibiotic therapy promotes the colonization of resistant strains in the vestibulum nasi but is not required for this. The kind of antibiotic therapy does not determine the entire pattern of resistance of the colonizing strain, but during antibiotic therapy the colonization will occur preferably with a strain of which one of the facets of the resistance pattern will agree with the therapy instituted at that time.

In addition to antibiotic therapy, there are probably other factors which are also of importance in determining whether colonization with resistant staphylococci in patients will occur. This can be deduced by combining the data from Table 4 and Table 6. In the latter Table are reported the data regarding the type of Staphylococcus present at discharge and the frequency with which these patients had received antibiotic therapy.

The data from Table 4 show clearly that the shift to the resistant hospital flora takes place especially in the first two weeks after admission. After that the relative distribution of patients discharged with a sensitive, a resistant, or no pathogenic Staphylococcus remains fairly constant. From Table 6 it appears that during each period the patients leaving hospital with a sensitive Staphylo-

TABLE 6.—*Correlation Between Antibiotic Treatment of Any Kind and Type of Staphylococci Found in the Vestibulum Nasi of Patients at Moment of Discharge*

	Duration of Stay in Hospital				
	1-7 Days	7-14 Days	2-4 Wk.	Longer	Total
Antibiotic-sensitive pathogenic strains					
No. patients	66	20	17	10	113
Antibiotic therapy in	4	10	11	6	31
% having received antibiotic therapy	6%	50%	65%	60%	27%
Antibiotic-resistant pathogenic strains					
No. patients	43	70	70	41	224
Antibiotic therapy in	10	59	64	39	172
% having received antibiotic therapy	23%	84%	91%	95%	77%
S. albus or no staphylococci					
No. patients	103	88	37	22	250
Antibiotic therapy in	19	60	30	21	130
% having received antibiotic therapy	18%	68%	81%	96%	52%
Total					
No. patients	212	178	124	73	587
Antibiotic therapy in	33	129	105	66	333
% having received antibiotic therapy	16%	73%	85%	90%	52%

coccus aureus have received antibiotic therapy less frequently than those leaving hospital with a resistant one. The frequency is also less than the average for all patients together, whereas in those patients leaving hospital with a resistant strain the frequency is higher than the average. In patients leaving hospital without a pathogenic Staphylococcus in the vestibulum nasi, the therapy rate is equal to the average. It may be assumed, however, that the antibiotic therapy has been spread equally over all patients who entered hospital, independent of the fact as to whether they carried a sensitive, a resistant, or no Staphylococcus at all in the vestibulum nasi on admission, as the therapy was not directed against the carriage of staphylococci in the vestibulum nasi but against a surgical affection not directly related herewith. The lower frequency of therapy in those who left hospital with a sensitive Staphylococcus indicates therefore that part of the patients who were harboring a sensitive Staphylococcus have exchanged this strain for a resistant one during therapy.† After the second week, however, the situation seems to stabilize to the effect that the carrier rate of sensitive staphylococci remains the same (Table 4), whereas the frequency of therapy is still increasing (Table 6). This last fact could be explained by assuming that in part of the patients the affinity to the sensitive Staphylococcus present in their vestibulum nasi is so great (folliculitis of the vibrissae, anatomical anomaly?), that the same is dispelled with difficulty by antibiotic therapy. It is possible that these patients belong to the group of constant carriers to which we shall return later.

There is a gradual decrease in the percentage of patients who are discharged without pathogenic staphylococci up to the period of two to four weeks of hospitalization, after which a stabilization occurs (Table 6). This shows that after admission part of this group of patients is lost to the group discharged with a resistant Staphylococcus. However, as mentioned already, the percentage of the patients discharged without a Staphylococcus and having received antibiotic therapy is about as high as the average for all patients together.‡ The combination of these two facts indicates that the colonization with resistant staphylococci in this group of patients is not influenced by antibiotic therapy but is probably based on a free interchange with resistant staphylococci from the hospital microflora, independent of antibiotic therapy. The stabilization which occurs in the percentage of the patients discharged without a Staphylococcus after the second week of hospitalization, notwithstanding a further increase in the percentage of those having received antibiotic therapy, could be explained by assuming that in part of these patients there is possibly such a slight inclination toward colonization with staphylococci in general that they even withstood the pressure of colonization by the host of resistant staphylococci in the hospital. Before their admission these patients probably belonged to the group of the constant "noncarriers," to which we shall also return latter.

3. *Carrier Rate of Pathogenic Staphylococci in Patients After Discharge.*—(*a*) Patients Harboring Penicillin-Resistant Staphylococcus at Time of Discharge: The fate of these penicillin-resistant staphylococci could be followed up in 63 patients. The results have been summarized in Table 7. From this Table it appears that there is a constant loss of the penicillin-resistant strains taken along from the hospital (group: same strain, resistant). In no case there was an indication that the original

† Statistical analysis of Tables 4 and 6 according to the χ^2-test shows that the differences in frequency of therapy between those leaving hospital with a sensitive and with a resistant Staphylococcus are statistically significant and that antibiotic therapy promotes colonization with a resistant Staphylococcus in a significant manner ($P=0.001$).

‡ The small difference in frequency of therapy in this group of patients with the average figures for therapy frequency are statistically not significant (with use of the χ^2-test, $P=0.80$).

TABLE 7.—*Follow-Up of Nasal Carriers of Penicillin-Resistant Strains of S. Aureus in Discharged Patients*

	At Discharge		0-2 Wk.		2-4 Wk.		4-6 Wk.		6-8 Wk.		8-10 Wk.		10-12 Wk.		3-6 Mo.		6 Mo.-1 Yr.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. examined	64		50		56		53		51		50		47		50		43	
Same strain, resistant	64	100	42	84	37	66	30	56.5	23	45	18	36	15	32	12	24	6	14
Same strain, sensitive	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
New strain, resistant	0	0	1	2	1	2	1	2	1	2	1	2	1	2	1	2	0	0
New strain, sensitive	0	0	0	0	1	2	5	9.5	7	14	8	16	5	11	3	6	2	5
Total carriers of pathogenic staphylococci	64	100	43	86	39	70	36	68	31	61	27	54	21	45	16	32	8	19
No staphylococci or S. albus	0	0	7	14	17	30	17	32	20	39	23	46	26	55	34	68	35	81

penicillin-resistant hospital strain lost its resistance and became sensitive to penicillin (group: same strain, sensitive). In 16 patients a sensitive Staphylococcus differing in phage type from the original resistant strain was found temporarily or permanently after the loss of the resistant strain. In three patients a resistant Staphylococcus, other than the one found at the time of discharge, could be demonstrated temporarily. In all three cases the newly acquired strain belonged to the phage Type 44B. In two of these cases the strain was acquired from a family member, who had probably acquired this strain himself while visiting the patient in hospital. In one case the source was not clear.

In many patients, however, the resistant Staphylococcus strains which have been lost are not replaced by other Staphylococcus strains, either sensitive or resistant ones. This results in a decrease of the total carrier rate of pathogenic staphylococci, besides the decrease in the carrier rate of resistant staphylococci already mentioned.

As it appears in Table 1, the patients who carry a penicillin-resistant Staphylococcus at discharge represent about 40% of the total number of discharged patients. One has therefore to multiply the figures for the carrier rate of resistant staphylococci from Table 6 by 0.4 in order to calculate how large the percentage of remaining hospital strains would have been among the total group of discharged patients. On account of the results obtained, it appears that in the period of three to six months the percentage of carriers of penicillin-resistant strains (0.4 times 24% is 9.6%) is still about twice as high as in a normal population as represented by the family members, in which this percentage amounts to 3% to 5% (Table 14.) It is not before a period of six months to one year that the percentage falls to almost normal (0.4 times 14% is 5.6%).

It may be observed that at the time at which the percentage of carriers of resistant strains in this group has become normal the total carrier rate of pathogenic staphylococci is lower than that of a normal population group, namely, 19% against 32% to 35% (Table 14). This fact could form an indication that the colonization with resistant hospital strains occurs mainly in patients who have been variable carriers also before their admission in hospital.

(*b*) Patients Harboring a Penicillin-Sensitive Strain at the Time of Discharge: A follow-up study was made of 21 persons who were discharged from the hospital while harboring a penicillin-sensitive Staphylococcus. These strains were also sensitive to all other antibiotics. The results obtained are shown in Table 8. From this Table it appears that the loss of penicillin-sensitive strains occurs at a slower rate than that of penicillin-resistant ones. After three to six months 44.5% of the sensitive strains originally present are still present, against only 24% at this date in the resistant group

TABLE 8.—*Follow-Up of Nasal Carriers of Penicillin-Sensitive Strains of S. Aureus in Discharged Patients*

	At Discharge		0-2 Wk.		2-4 Wk.		4-6 Wk.		6-8 Wk.		8-10 Wk.		10-12 Wk.		3-6 Mo.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. examined	21		17		20		16		14		13		13		9	
Same strain, sensitive	21	100	17	100	15	75	12	75	10	71.5	8	62	8	62	4	44.5
New strain, resistant	0	0	0	0	1	5	0	0	0	0	0	0	0	0	0	0
New strain, sensitive	0	0	0	0	0	0	1	6	1	7	1	7	1	7	1	11
Total of carriers of pathogenic staphylococci	21	100	17	100	16	80	13	81	11	78.5	9	69	9	69	5	55.5
No staphylococci or S. albus	0	0	0	0	4	20	3	19	3	21.5	4	31	4	31	4	44.5

(Table 9).§ This indicates that among this group of patients there are more persons who show an inclination to regular carriership and possibly for that reason have been able to preserve even the sensitive staphylococci which they harbored on admission to hospital.

Only once was a resistant strain recovered from this group of patients. This strain was penicillin- and streptomycin-resistant and belonged to phage Type 44B. It was found only at one examination, being replaced the next time by a sensitive one which differed, however, from the strain originally carried by the patient. The origin of the resistant strain could not be determined.

(*c*) Patients Harboring Only a Staphylococcus Albus or No Staphylococci at All in the Vestibulum Nasi: From this group 53 discharged patients were followed up. The results obtained have been summarized in Table 9.

It appears from this Table that also after discharge resistant staphylococci were found only in a small percentage in these patients. In three of the four cases in which a resistant Staphylococcus could be demonstrated temporarily afterward it could be traced to the fact that they had visited the outpatient department of the clinic after discharge. The phage type was 44B in all three cases, the resistance applying to penicillin only. In the fourth patient the origin of the resistant strain could not be traced. Besides the nearly complete absence of penicillin-resistant staphylococci, it is also striking that the total carrier rate of pathogenic staphylococci remained low in this group during the period of observation. In the period of 10 to 12 weeks after discharge only 8% harbored staphylococci, against 45% in those who left the hospital with a resistant Staphylococcus and 69% in those who did so with a sensitive Staphylococcus (Tables 7 and 8). The carrier rate in the group of

§ Statistical analysis of the data obtained at the various consecutive periods of examination shows that these differences in the rate of decrease of the strains originally present are statistically valid ($P<0.05$).

TABLE 9.—*Follow-Up of Carrier Rate of Pathogenic Staphylococci in Patients Discharged Without Pathogenic Staphylococci in Vestibulum Nasi*

	At Discharge		0-2 Wk.		2-4 Wk.		4-6 Wk.		6-8 Wk.		8-10 Wk.		10-12 Wk.		3-6 Mo.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. examined	53		49		45		41		33		31		24		8	
S. albus or no staphylococci	53	100	47	96	44	98	39	95	30	91	29	94	22	92	5	63
S. aureus resistant	0	0	2	4	0	0	2	5	2	6	2	6	2	8	2	25
S. aureus sensitive	0	0	0	0	1	2	0	0	1	3	0	0	0	0	1	12
Total no. of pathogenic staphylococci	0	0	2	4	1	2	2	5	3	9	2	6	2	8	3	7

household contacts belonging to this group of discharged patients is, however, essentially the same as in the other discharged patients, and yet the tendency to acquire a pathogenic Staphylococcus from the surrounding staphylococcal flora seems less than in the other groups. If we figured the total number of "free weeks" in each group before the patients attracted a new strain after having lost their own strain, or after discharge in case no strain had been present at that time, against the number of strains acquired after these "free weeks" we came to the following data. In the group of patients discharged from hospital with a resistant strain, 18 new strains were acquired by 37 patients after a total of 190 weeks, i. e., 1 new strain on an average of 10 "free weeks." In the group of patients discharged without a pathogenic Staphylococcus, only six new strains were acquired by 50 patients in 354 weeks, i. e., one new strain on an average of nearly 60 "free weeks."‖ In the group of patients discharged with a sensitive Staphylococcus, the number of patients who could be followed long enough was too small to give a reliable figure (only five patients for 27 weeks in which two new strains were attracted). This slight inclination of the group of patients who were discharged without a pathogenic Staphylococcus to acquire a new strain does give rise to the thought that these persons who also had withstood the contaminating influence of the hospital surrounding belonged to the group of the constant "noncarriers" in the population.

(*d*) Strains Resistant to Streptomycin, Chlortetracycline, and Oxytetracycline: Though resistance to these antibiotics occurred only in strains which were also resistant to penicillin, this did not necessarily mean that the loss of penicillin-resistant strains in itself should result in a parallel loss of resistance to other antibiotics. On the one hand, multiple resistant strains might get lost more quickly or more slowly than strains resistant to penicillin only; on the other hand, the possibility should be left open that resistance to streptomycin or to chlortetracycline and oxytetracycline might be lost without loss of the strain.

From Tables 10 and 11 it appears, however, that in general the rate of resistance to these antibiotics decreases in the same way as for the strains resistant to penicillin. As with penicillin, the decrease in the resistance rate to streptomycin, chlortetracycline, and oxytetracycline was nearly entirely due to loss of the resistant strain. In only two strains was there a reversal of resistance to chlortetracycline and oxytetracycline to sensitivity to these antibiotics, the strains remaining present. In all other strains resistance to streptomycin, chlortetracycline, and oxytetracycline remained present as long as the strains could be cultured.

‖ The difference between these figures is statistically significant according to the χ^2-test ($P<0.001$).

TABLE 10.—*Follow-Up of Carriers of Streptomycin-Resistant Strains of S. Aureus in Vestibulum Nasi in Discharged Patients*

	At Discharge		0-2 Wk.		2-4 Wk.		4-6 Wk.		6-8 Wk.		8-10 Wk.		10-12 Wk.		3-6 Mo.		6 Mo.-1 Yr.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. examined	53		42		46		42		40		39		37		40		32	
Same strain, resistant	53	100	36	86	31	67.5	25	59.5	18	45	14	36	11	30	9	22.5	5	15.5
Same stain, sensitive	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
New strain, resistant	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
New strain, sensitive	0	0	1	3.5	2	4	6	14.5	8	20	7	18	6	16	3	7.5	0	0
Total carriers of pathogenic staphylococcus	53	100	37	89.5	33	71.5	31	74	26	65	21	54	17	46	12	30	5	15.5
No staphylococci or S. albus	0	0	5	12	13	28.5	11	26	14	35	18	46	20	54	28	70	27	84.5

TABLE 11.—*Follow-Up of Carriers of Chlortetracycline- and Oxytetracycline-Resistant S. Aureus in Vestibulum Nasi in Discharged Patients*

	At Discharge		0-2 Wk.		2-4 Wk.		4-6 Wk.		6-8 Wk.		8-10 Wk.		10-12 Wk.		3-6 Mo.		6 Mo.-1 Yr.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. examined	36		26		30		26		26		24		25		27		21	
Same strain, resistant	36	100	21	81	17	57	14	54	9	34	6	25	5	20	3	11	2	10
Same strain, sensitive	0	0	0	0	1	3.5	0	0	1	4	0	0	0	0	0	0	0	0
New strain, resistant	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
New strain, sensitive	0	0	1	4	2	6.5	4	15	8	31	6	25	6	24	3	11	0	0
Total carriers of pathogenic staphylococci	36	100	22	85	20	67	18	69	18	69	12	50	11	44	6	22	2	10
No staphylococci or S. albus	0	0	4	15	10	33	8	31	8	31	12	50	14	56	21	78	19	90

Generally the resistance to streptomycin stayed on the same level as present at the time of discharge. Twenty-three strains were inhibited by 1000μg. or more per milliliter; two strains, by 500μg. per milliliter; six strains, by 100μg. per milliliter; four strains, by 25μg. per milliliter. Only in one strain, which was originally inhibited by more than 1000μg. per milliliter, this sensitivity reversed to 50μg. per milliliter in the sixth to the eighth week, at the same time with the reversion from resistance to chlortetracycline and oxytetracycline to sensitivity to these antibiotics.

The resistance to oxytetracycline remained at 250μg. or more per milliliter in nearly all strains. In one strain the resistance decreased from more than 250μg. per milliliter to 25μg. per milliliter at the same time at which this strain, originally chloramphenicol-resistant, became also sensitive to this antibiotic. The same phenomenon occurred in a second strain in which the resistance changed from more than 250μg. per milliliter to 50μg. per milliliter. The decrease in resistance to oxytetracycline in these two strains went together with a decrease in resistance to chlortetracycline, namely, from 75μg. per milliliter to 20μg. per milliliter in both cases. In the other 18 strains, resistant to chlortetracycline, the level of resistance remained in 12 strains at 150μg. per milliliter; in 4 strains, at 75μg. per milliliter; in 2 strains, at 50μg. per milliliter. Two strains lost their resistance to chlortetracycline and oxytetracycline completely. They were originally inhibited by 150μg. and 35μg., respectively, of the former antibiotic per milliliter and both by more than 250μg. per milliliter of the latter. After their reversion they were both inhibited by 0.5μg. of chlortetracycline per milliliter and 5μg. of oxytetracycline per milliliter. The change from resistant to sensitive occurred in one step. The phage type of the one strain was 6/7/47/53/54/75/77 and of the other strain, 6/47/53/75/77. In one strain the reversal occurred concurrently with a reversal of chloramphenicol resistance to sensitivity; the other had always been sensitive to chloramphenicol.

After three to six months 22.5% of the streptomycin-resistant hospital strains were still present; after six months to one year, 15.5%. As the patients harboring streptomycin-resistant strains at discharge represented 30% of the total number of discharged patients, this means that three to six months after discharge nearly 7% (0.3 times 22.5%) of the patients will still carry a streptomycin-resistant Staphylococcus strain; after six months to one year, 4.5%. For chlortetracycline and oxytetracycline these figures are 2% (0.2 times 11%) and 2%. As the pathogenic staphylococci among the normal population in the Netherlands, so far as no contact with the hospital has existed, show streptomycin resistance only rarely and never resistance to chlortetracycline and oxytetracycline, it is clear from

TABLE 12.—*Follow-Up of Carriers of Choramphenicol-Resistant Strains of S. Aureus in Vestibulum Nasi in Discharged Patients*

	At Discharge		0-2 Wk.		2-4 Wk.		4-6 Wk.		6-8 Wk.		8-10 Wk.		10-12 Wk.		3-6 Mo.		6 Mo.-1 Yr.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. examined	18		10		13		13		13		12		10		14		15	
Same strain, resistant	18	100	7	70	7	54	5	38	1	8	1	8	1	10	0	0	0	0
Same strain, sensitive	0	0	1	10	1	8	2	15	4	31	2	17	1	10	1	7	1	7
New strain, resistant	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
New strain, sensitive	0	0	1	10	1	8	2	16	4	31	3	25	2	20	1	7	0	0
Total carriers of pathogenic staphylococci	18	100	9	90	9	70	9	70	9	70	6	50	4	40	2	14	1	7
No staphylococci or S. albus	0	0	1	10	4	31	4	31	4	31	6	50	6	60	12	86	14	93

this fact that hospitalization still shows its unfavorable effect until a year after discharge.

(*e*) Chloramphenicol-Resistant Strains: Though resistance to chloramphenicol in our material occurred also only in strains which were also penicillin-resistant and therefore the same applies here as in the case of strains resistant to streptomycin, chlortetracycline, and oxytetracycline, we want to discuss them separately, as in our material the phenomenon of back-mutation to sensitivity occurred more frequently in chloramphenicol-resistant strains than in strains resistant to the other antibiotics.

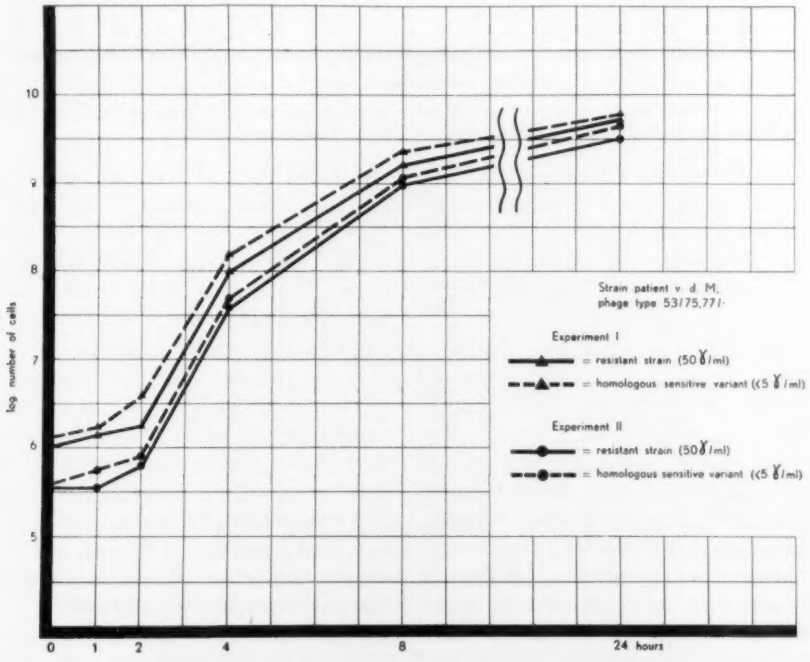
The results obtained in connection with resistance to chloramphenicol are summarized in Table 12. From this Table it seems clear that the percentage of chloramphenicol-resistant strains decreases far more rapidly than noted for the other antibiotics. This is based on the fact that in 8 of the 18 patients the strain became again sensitive to chloramphenicol before being lost by the patient. The difference in the decrease between penicillin- and streptomycin-resistance rate, on the one hand, and chloramphenicol-resistance rate, on the other hand, was statistically significant with the use of the χ^2-test ($P=0.01$). The difference between the decrease in chloramphenicol resistance and tetracycline resistance was, with the small number of strains which could be followed up, statistically not valid. However, in addition to this back-mutation in vivo we noticed the same also in part of the strains in vitro when we subcultured them regularly on culture media not containing antibiotics. We could demonstrate this in another 16 of 32 chloramphenicol-resistant strains recovered from as many discharged patients who could not be followed. However, of 85 strains resistant to the tetracyclines, only 2 showed such a reversal to sensitivity in vitro under the same condition. The difference between these figures is statistically significant ($P=0.001$). We have to realize, however, that although we speak of strains, they are really only various isolates of, genetically speaking, only a few strains circulating in hospital as proven by phage typing.

The phage types of the chloramphenicol-resistant strains which were subject to back-mutation in vivo were as follows: Four strains belonged to Type 53/75/77; two strains, to Type 6/7/47/53/54/75/77, and two strains, to type No. In the group of strains which showed the back-mutation in vitro, the distribution of the phage types was as follows: 10 strains of Type 53/75/77 and 6 strains of Type 6/7/47/53/54/75/77. So the phenomenon was not restricted to one phage type. Before the back-mutation these strains were inhibited, like all other chloramphenicol-resistant strains in our material, by 50μg. per milliliter and not by 25μg. per milliliter; after the back-mutation, by 5μg. per milliliter and not by 2.5μg. per milliliter. The reversal to sensitivity occurred in all strains in one step.

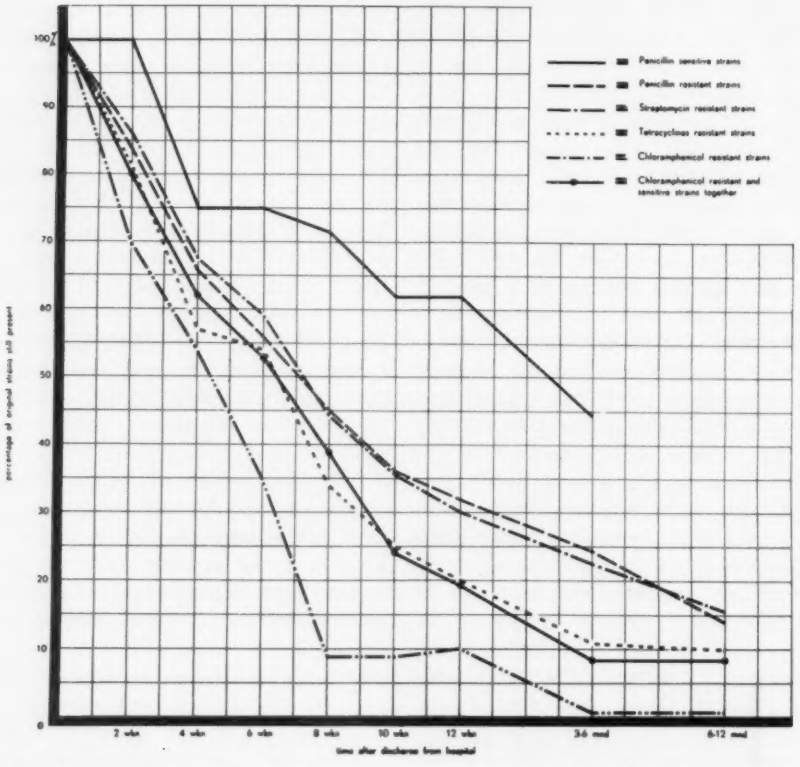
In culture of the patients' strains, only one colony was picked for study. Therefore the possibility existed that at the time of the first isolation of sensitive colonies these could have been present next to resistant colonies but had been missed by the technique chosen for this study. It was then surprising, however, that consecutive isolations in none of the 13 possibilities present showed any sensitive colony between times, while after the first isolation of a sensitive variant there was never a recurrence of a resistant one. This rather sudden shift to sensitivity could suggest that the sensitive cells, when once present, had a better possibility of developing in the human being than the resistant cells, overgrowing the resistant bacteria still present, such as is assumed also for various other bacteria. In vitro experiments, however, did not show any difference in the growth curves in liquid medium of equivalent inoculums of a resistant and a sensitive variant of the same strain, as can be seen from Graph 1.

Besides the back-mutation to chloramphenicol sensitivity, the phenomenon of loss of resistant strains occurred also for chloramphenicol-resistant strains. In principle the frequency of the loss of the hospital strain was as high in the case of the strains originally resistant to chloramphenicol as in the case of the strains resistant to the other antibiotics. For if the strains which continued to be chloramphenicol-resistant, are added to those "hospital" strains which had become sensitive to chloramphenicol, the percentage of all "hospital" strains together decreases in the same manner as had been observed for the strains resistant to the other antibiotics.

The phenomenon of back-mutation together with the loss of the strains, which both are effective in the same direction, resulted in the fact that in the discharged patients no chloramphenicol-resistant strains were present any more in the period after



Graph 1.—Growth curves of chloramphenicol-resistant strain and its sensitive variant in liquid medium. Comparable results, not reproduced here, were obtained in two other strains.



Graph 2.—Follow-up of nasal carrier rate of antibiotic-sensitive and antibiotic-resistant staphylococci in discharged patients. Wkn indicates weeks; mnd, months.

three months. So the influence of hospitalization on the resistance to chloramphenicol has disappeared completely after three months. The course of resistance to the various antibiotics has been graphically summarized in Graph 2.

4. *Carrier Rate of Pathogenic Staphylococci and Percentage of Antibiotic-Resistant Staphylococci in Vestibulum Nasi of Family Members of Discharged Patients.*—Examination of 455 family members of 138 patients was carried out. In 369 family members of 117 patients, the follow-up could be started at and carried on from the first period of examination. Eighty-six family members were not present at the moment of discharge of the patient. They could, however, be examined from a later date on. In case a resistant Staphylococcus was found the first time that these family members were examined, it was not possible as a matter of fact to decide whether or not this resistant Staphylococcus had already been present at the moment that the patient was discharged or when it had been acquired. The results obtained in this group of family members were therefore not used in computing the average figures for the various periods of examination. However, these results gave us sometimes some added information on the possibility of transfer of a resistant Staphylococcus from a patient to a family member in the last part of the examination period. Where necessary, these data will be mentioned separately.

The distribution of the phage types in the strains of the 369 family members as found at the first isolation was as is shown in

TABLE 13.—*Distribution of Phage Types in Strains of Family Members of Discharged Patients as Found at the First Isolation*

	Total	Phage Group or Type													
		Group I		Group II		Group III		44B		No		NS *		NT †	
	No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Sensitive strains	117	20	17.1	13	11.1	14	12.0	0	0	1	0.9	14	12.0	55	47.0
Resistant strains	11	1	9.1	0	0	6	54.5	2	18.2	1	9.1	1	9.1	0	0
Total	128	21	16.4	13	10.2	20	15.6	2	1.6	2	1.6	15	11.7	55	43

* NS indicates nonspecific pattern.
† NT indicates nontypable.

Table 13. The distribution of phage types in the group of sensitive strains is in general the same as in the sensitive strains of the discharged patients. The number of resistant strains is too small to put too much weight on the percentages found.

The family members were divided over the following groups: 142 belonged to 49 patients who were discharged with an antibiotic-resistant Staphylococcus; 60, to 16 patients who left the hospital with a sensitive Staphylococcus, and 167, to 52 patients who did not carry a pathogenic Staphylococcus at the moment of discharge. The results of the follow-up examinations are summarized in Table 14.

It follows from Table 14 that the carrier rate in the family members is not influenced to any considerable extent by the homecoming of the patient. The percentage of resistant staphylococci, though, is higher in the group of family members in which the discharged patient carried a resistant Staphylococcus than in the other two groups. It is clear that the origin of the resistant strains in the family members in many cases was not based on transfer of resistant staphylococci from the discharged patients, as these strains could also be found in family members of patients who did not carry any staphylococci in the vestibulum nasi at the moment of discharge. Yet, on closer examination of the origin of the strains, it showed that there was probably a greater influence of the hospital flora on the percentage of resistant staphylococci in the normal population than would follow from contamination by the discharged patients only. For this purpose we divided the strains according to their origin into the following groups.

(*a*) Transfer: A family member who did not carry a pathogenic Staphylococcus or a Staphylococcus of different pattern of resistance and phage type from that of the discharged patient attracted some time *after* discharge of the patient a strain identical in pattern of resistance and in phage type to that of the discharged patient.

(*b*) Transfer or Autoinfection: The family member already carried a resistant strain identical to that of the patient at the first examination, shortly before or very shortly after discharge of the patient. In these cases the strain could have been obtained by the family member by direct contact with the hospital microflora (inhalation of dust, touching objects in hospital) while visiting the patients or directly from the patient himself.

(*c*) Autoinfection: The family member had at the moment of discharge of the patient or attracted at some time afterward a resistant strain not identical to that of he discharged patient, but the family member had had a proven contact with the hospital sphere shortly before the presence of the resistant strain was noticed. This contact could have been (*a*) a visit to a relative who was hospitalized; (*b*) being examined at an outpatient department of a hospital; (*c*) being hospitalized himself.

(*d*) Unknown: This heading included all other cases, also those in which no further

TABLE 14.—*Follow-Up of Carrier Rate of Pathogenic Staphylococci in Vestibulum Nasi of Family Members of Discharged Patients*

Family Members Belonging to		0–1 Wk.		1–2 Wk.		2–4 Wk.		4–6 Wk.		6–8 Wk.		8–10 Wk.		10–12 Wk.		3–6 Mo.		6 Mo.–1 Yr.	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Patients diacharged with penicillin-resistant strain	No. examined	128		107		120		106		96		85		86		43		23	
	Pen.-resistant	6	4.7	6	5.6	4	3.3	5	4.7	5	5.2	5	5.9	8	9.4	3	7.0	3	13.0
	Pen.-sensitive	39	30.5	33	30.8	36	30.0	32	30.2	28	29.2	26	30.6	22	25.9	15	34.9	6	26.1
	Total pathog. staphylococci	45	35.2	39	36.4	40	33.3	37	34.9	33	34.4	31	36.5	30	35.3	18	41.9	9	39.1
Patients discharged with penicillin-sensitive strain	No. examined	60		51		54		50		35		32		30		14		1	
	Pen.-resistant	0	0	0	0	0	0	1	2.0	0	0	0	0	0	0	1	7.2	0	0
	Pen.-sensitive	16	26.7	15	39.4	17	31.5	19	38.0	17	48.5	7	21.8	9	30.0	3	21.4	1	100
	Total pathog. staphylococci	16	26.7	15	39.4	17	31.5	20	40.0	17	48.5	7	21.8	9	30.0	4	28.6	1	100
Patients discharged without staphylococci or with S. albus	No. examined	161		131		146		113		93		79		66		32		2	
	Pen.-resistant	5	3.1	4	3.0	5	3.4	5	4.4	4	4.3	4	5.1	3	4.6	2	6.3	0	0
	Pen.-sensitive	51	31.7	39	29.8	41	28.1	33	29.2	25	26.9	23	29.1	16	24.2	8	25.0	1	50
	Total pathog. staphylococci	56	34.8	43	32.8	46	31.5	38	33.6	29	21.2	27	34.2	19	28.8	10	31.3	1	50
Total	No. examined	349		289		320		269		224		196		182		89		26	
	Pen.-resistant	11	3.2	10	3.5	9	2.8	11	4.1	9	4.0	9	4.6	11	6.1	6	6.8	3	11.5
	Pen.-sensitive	106	30.4	87	30.1	94	29.4	84	31.2	70	31.2	56	28.6	47	25.8	26	29.2	8	30.8
	Total pathog. staphylococci	117	33.6	97	33.6	103	32.2	95	35.3	79	35.2	65	33.2	58	31.9	32	36.0	11	42.3

TABLE 15.—*Origin of Resistant Strains Found in Vestibulum Nasi of Family Members of Discharged Patients*

Origin of Strains	0-1 Wk.	1-2 Wk.	2-4 Wk.	4-6 Wk.	6-8 Wk.	8-10 Wk.	10-12 Wk.	3-6 Mo.	6 Mo.-1 Yr.
Total no. resistant strains	11	10	9	11	9	9	11	6	3
Transfer									
No.	0	2	0	1	0	1	2	2	2
% of total no. of res. strains	0	20	0	9.1	0	11.1	18.2	33.3	66.6
Transfer or autoinfection									
No.	3	1	1	1	1	1	1	0	0
% of total no. of res. strains	27.3	10	11.1	9.1	11.1	11.1	9.1	0	0
Autoinfection									
No.	5	4	5	4	4	3	4	2	0
% of total no. of res. strains	45.4	40	55.6	36.4	44.5	33.4	36.4	33.3	0
Unknown									
No.	3	3	3	5	4	4	4	2	1
% of total of res. strains	27.3	30	33.3	45.4	44.5	44.4	36.4	33.3	33.3

information could be obtained. In some of the latter the phage type of the strain indicated a contact with the hospital microflora, but this could not be verified by lack of objective information.

The part which each of these four groups played in the total figure for each examination period is summarized in Table 15.

From this Table it can be seen that during the whole period of the investigation more than one-half to two-thirds of the resistant strains originated from direct or indirect contact with the resistant hospital microflora.

One cannot read, however, from Table 15 the absolute number of family members which belonged to each of the separate groups. The figures for the consecutive examination periods do not always represent the same persons. These absolute numbers are as follows: transfer was responsible for a resistant strain in 8 family members belonging to 4 patients; autoinfection or transfer, in 3 family members belonging to 3 patients; autoinfection in 8 family members from 7 families. The origin was unknown in 13 family members belonging to 7 patients.

In the 86 family members belonging to 21 patients which were investigated only from a later date on the four groups were represented as follows: one case of transfer, six cases of transfer or autoinfection in connection with three patients, two cases of autoinfection in one family, one case unknown.

Therefore there were 28 cases in total in which contact with the hospital microflora, direct or indirect, was responsible for the presence of a resistant strain, against 14 of which the origin was not known. Of the 14 strains in which no contact with the hospital could be proven, all penicillin-resistant, three strains were also resistant to streptomycin. None was resistant to any of the other antibiotics. Of the 28 penicillin-resistant strains in which a contact with the hospital sphere was proven, 10 were streptomycin-resistant, but 6 were also resistant to the tetracyclines. This difference also reflects the difference in origin. The deficient hospital hygiene, causing the marked increase in antibiotic-resistant staphylococcal infections in the hospitals itself, extended, therefore, its influence also outside the hospital and was responsible for 67% of the resistant strains in this group of family members and household contacts. This group, although in the large majority consisting of normal people, is not a true representation of the general population. Grouped together around discharged patients, they had had thereby a more intensive contact with the hospital sphere than a random sample of the general population would have had. Although the danger of contamination of the general population by the resistant hospital microflora is therefore probably less than would follow from the high figure in this

group of family members of discharged patients, it cannot be disregarded.

Although the number of direct transfers was small, its influence also cannot be neglected entirely. The nine cases mentioned above occurred in a total of 5 families of the group of 62 families with 189 members in which this possibly was present (i. e., belonging to patients discharged with a resistant Staphylococcus). This means that transfer took place in 5% of the family members and in 8% of the families. If one includes the cases of "transfer or autoinfection," these figures would be as follows: in 7% of the family members and in 11% of the families. As the patients discharged with a resistant strain formed only 40% of the total number of discharged patients, the maximal effect of transfer would come to around 3% of the family members and in 4.5% of the families of all the discharged patients together. In many cases, however, this transfer of a resistant strain will have only a temporary, sometimes even very transitory, effect. In four of the cases mentioned the transferred resistant strains were present at only one examination and had disappeared again at the next biweekly investigation. In four cases the strain was present longer than four weeks (in two cases more than five months). In six cases the family member concerned could not be followed up after the transfer had taken place, mostly because of the fact that the transfer took place late in the period of observation.

Besides the transfer from discharged patients to household contacts, transfer from household contacts to discharged patients was observed with certainty in 9 of 81 patients in whom there were one or more Staphylococcus carriers in the family. In eight cases this was a sensitive strain; in one case, a resistant strain. Furthermore, seven patients acquired a new sensitive Staphylococcus, not typable by phages, while a nontypable sensitive Staphylococcus was also present in one of their family members. Although transfer from family member to patient could also have been responsible for this acquisition of a new strain by the discharged patient, this could for that reason not be proven or denied.

5. *Duration of Carriership of Pathogenic Staphylococci in Individual Members of a Normal Population.*—Various investigations [16,31,32] have shown already that the members of a normal population can be divided into persons who are more or less constant carriers of pathogenic staphylococci, those who are irregular carriers, and a third group in which pathogenic staphylococci are almost never found in the vestibulum nasi. Our material gave a good opportunity to confirm the validity of this subdivision on rather extensive material.

TABLE 16.—*Continuity of Carriership of Pathogenic Staphylococci in Vestibulum Nasi in Members of a Normal Population*

	No. of Consecutive Examination Periods, 2 Wk. Each							
	5		6		7		8	
% of Positive Culture Found at Consecutive Examinations	No. Persons	% of Total Examined	No. Persons	% of Total Examined	No. Persons	% of Total Examined	No. Persons	% of Total Examined
0	123	50.6	94	50.5	75	51	33	47.2
1-20	25	10.3	15	8.1	14	9.5	6	8.6
21-40	14	5.8	11	5.9	5	3.4	4	5.7
41-60	5	2.1	6	3.2	10	6.8	2	2.9
61-80	17	7	5	2.7	1	0.7	1	1.4
81-99	0	0	12	6.5	6	4.1	5	7.1
100	59	24.3	43	23.1	36	24.5	19	27.1
Total persons examined	243	100	186	100	147	100	70	100

Table 16 represents the distribution of the family members (in percentages of the total number examined) according to the frequency (0%, 1%-20%, 21%-40%, etc.) in which pathogenic staphylococci were present in their vestibulum nasi at five, six, seven, and eight consecutive biweekly examinations, respectively.

Table 16 shows that for all numbers of consecutive examinations about 25% of the people examined are constant carriers, against about 50% in which a pathogenic Staphylococcus was never present. This leaves about 25% for irregular carriers. The latter are, however, distributed too irregularly over the various frequency figures for them to be defined as a definite separate group.

Comment

It is certain that the presence in the vestibulum nasi of pathogenic staphylococci, also of antibiotic-resistant staphylococci, does not have to have any clinical significance for the person concerned. Many investigations [31-35] have shown that about 30%-60% of normal persons carry pathogenic staphylococci in their vestibulum nasi without having a clinical staphylococcal infection at that moment or having had such an infection shortly before. However, if a staphylococcal infection of the skin occurs in a carrier, it is generally accepted that the Staphylococcus present in the vestibulum nasi is very often identical to that present in the skin lesion and may have been the causal agent.[36-38]

The importance of the carriership of pathogenic staphylococci in the vestibulum nasi as a causative factor in the occurrence of hospital cross infections has not been determined precisely. While on the one hand this carriership is considered as being a decisive factor (Gould and Allan [27]), others (as, for example, Barber and Burston [3]) do think that the carrier rate in the vestibulum nasi is more a reflection of than the cause for the occurrence of hospital infections. However, also with the last conception, it is true that the percentage of infections with resistant staphylococci runs parallel to the percentage of resistant staphylococci present in the vestibulum nasi. One can state, therefore, that in the individual case as well as from an epidemiological standpoint the distribution of the antibiotic sensitivity in the nasal strains may give us some information as to how far antibiotic therapy may be feasible in the individual patient as well as in the population under consideration.

The results of our investigations confirm in general those already previously published in which the increased nasal carrier rate of hospitalized patients with antibiotic-resistant staphylococci is mainly seen as an interchange with or a colonization by resistant strains from the hospital microflora and not as a resistance due to mutation and selection by antibiotic therapy in the patient himself. However, the colonization occurs by preference in those patients who receive antibiotic therapy, although it was impossible to predict with any certainty the total pattern of resistance of the colonizing strain from the type of antibiotic treatment which the patient received. In 84% of the cases the pattern of resistance, seen as a whole, did indeed not agree with the antibiotic therapy given. This figure expresses clearly the fact that the pattern of the resistance of the colonizing strain is mainly dictated by the pattern of resistance of the hospital staphylococci which are circulating at that moment in the hospital or department concerned. In our material this was shown most clearly in the resistance against the tetracyclines. Although this antibiotic was used and had been used also in the previous years on a restricted scale on the surgical wards and much less frequently than chloramphenicol, the resistance rate against the tetracyclines was definitely higher than against chloramphenicol. The conclusion from this fact is that when a patient shows a staphylococcal infection shortly after discharge from hospital the anamnesis regarding the antibiotic therapy

he has received during hospitalization will not give us any real information regarding the pattern of sensitivity and resistance of the infecting Staphylococcus.

Two factors seem responsible for the contrast between the rate for chloramphenicol resistance and tetracycline resistance:

1. The known fact that staphylococci become less readily and to a smaller degree resistant to chloramphenicol than to the tetracyclines. In our material also resistance against chloramphenicol never reached a higher figure than 50μg. per milliliter, that is, about 10-20 times the normal sensitivity, while the resistance against the tetracyclines often was in the range of 150μg.-250μg. per milliliter, that is, about 200-300 times the value for the normal sensitive strains.

2. The tendency noticed in part of the chloramphenicol-resistant strains to mutate back to normal sensitivity. This phenomenon has also been described by Chabbert and Debruge,[39] so that it seems to be of more than incidental importance. It is certainly not the property of one type of strain only, as the strains showing this phenomenon in our material belonged to three phage types. The observation made by Gibson and Thompson[40] that the resistance rate against chloramphenicol in strains cultivated from patients in a burns ward dropped much faster after stopping chloramphenicol therapy on the wards entirely than the resistance rate against the tetracyclines after stopping the latter would also fit in this pattern.

The phenomenon of back-mutation was also noticed in some tetracycline-resistant strains but in much lower frequency than for chloramphenicol resistance. Furthermore, with one exception, the loss of tetracycline resistance was always correlated to the loss of chloramphenicol resistance. On the other hand, loss of chloramphenicol resistance occurred many times without loss of resistance to the tetracyclines. The genetic stability of the chloramphenicol-resistant mutants seems therefore to be less than of the tetracycline-resistant mutants.

Besides the promoting effect of antibiotic therapy, the colonization of the vestibulum nasi by resistant strains seems also to be influenced by a personal factor of the patient. There are certain indications in our material that in the group of the "constant carriers," on the one hand, and in the group of the "constant noncarriers," on the other hand, there are certain people who are in some way "resistant" to colonization by a (resistant) Staphylococcus from the surrounding microflora, even under antibiotic therapy. It seems possible that especially the group of the variable carriers contributes to the increase in the percentage of the nasal carrier rate of resistant staphylococci in hospitalized patients. For this reason they will form also the most dangerous group in the spread of the resistant staphylococci through the hospital. It seems improbable, however, that such a knowledge ever could have practical importance, as it will be nearly impossible to know to which group the patient belongs at the moment of admission.

Besides an increase of the resistance rate in nasal carriers, we also observed in our material an increase in the total percentage of nasal carriers during hospitalization. This is in accordance with the data of Barber et al.[41,42] and Brodie[43] but in contrast with those of Lepper et al.,[9] who found a significant increase only in those patients who received chlortetracycline (Aureomycin) therapy, and Knight et al.,[44] who did not see any increase in patients who were hospitalized less than 30 days and only a slight increase when hospitalization lasted up to 60 days. Furthermore, the carrier rate found by these last-named authors was much lower (about 20%) than ours. The cause for these differences can lie in various factors:

1. Differences in method of cultivation, as mentioned already by Knight et al.,[44] themselves. With one method it may be possible to prove the presence of only a rare Staphylococcus which may get lost with another method. In our material 25%

of the carriers gave a nearly pure culture of staphylococci on the blood-agar medium; in 27% there were 50-200 colonies; in 25%, 10-50 colonies, while in 27% there were only a few colonies.[1-10] Wallmark,[45] by example, found heavy growth in 65 of his 182 cultures, moderate growth in 44, and a few colonies in 77. Vogelsang[46] counted two-thirds of his carriers in the heavy carrier group.

2. Differences in the measure of and the way in which the cross infection takes place in the various hospitals (dust, direct contact with patient, nurse, type of patients, etc.). Our figures were obtained on a surgical department, where most patients were nursed on large wards containing 17-20 beds. The results of Lepper et al. are related to patients nursed in a hospital for contagious diseases in which the nursing is more adjusted to the prevention of cross infection than on a surgical ward, in which the patients are considered as not contagious. Furthermore, the patients in a hospital for contagious diseases are nursed more frequently on small wards or in special cubicles. That separate nursing in itself may be of importance follows from the figures of Howe,[47] who saw a smaller percentage of wound infection in private patients in separate rooms than in patients on a ward.

Although the causes for these differences cannot be pointed out with certainty, it is clear that a hospital with a high carrier rate of resistant staphylococci in discharged patients forms a potentially greater danger for spread of these staphylococci in the normal population than a hospital in which this carrier rate is low. A more accurate comparison than is now possible from the literature of the circumstances under which great differences in the carrier rate of resistant staphylococci are found in various hospitals might contribute to our insight into which factors play the most important part in the spread of these micro-organisms.

The follow-up of discharged patients showed that for a considerable time the nasal carrier rate for antibiotic-resistant staphylococci stayed at a higher, although gradually decreasing, level than is found in a normal population. This means that if a staphylococcal infection develops in such a patient there is a higher risk than usual that such an infection will be caused by a resistant Staphylococcus. This might be of special danger in case such an infection has a fulminating character, as in staphylococcal pneumonia complicating influenza, as the choice of the right antibiotic therapy becomes rather difficult. As stated already, the pattern of resistance of such a strain cannot be deduced with any certainty from the antibiotic therapy previously received. The best choice for starting treatment in such cases probably would be a combination of erythromycin and chloramphenicol, the former because the resistance rate against this antibiotic is generally still rather low and the latter because the resistance against that antibiotic is lost quickly. The combination will cover nearly all probabilities till the sensitivity tests will have shown the true pattern of resistance.

Ultimately though the carrier rate for penicillin-resistant staphylococci becomes normal 6-12 months after discharge, while chloramphenicol resistance was lost entirely after 3 months in our material. The danger of resistance against streptomycin and the tetracyclines seems to linger longer and, though on a restricted scale, was still present one year after discharge.

Transfer of hospital staphylococci from patients to household contacts does not occur frequently. However, it cannot be neglected entirely as a cause for the dissemination of resistant staphylococci. We found such a transfer in 11% of the families and in 8% of the household contacts of those patients who were discharged with a resistant Staphylococcus. As Dowling et al.[18] found such a transfer in 13% of the families investigated, there is a good correlation between these results. However, the phenomenon is of less importance than would follow from these figures. The patients who were dis-

charged with a resistant Staphylococcus represented only a part of all the discharged patients. Taking this into consideration, one comes to a transfer in 4.5% of the families and in 3% of the household contacts. Furthermore, the duration that the transferred strain was present in the family member was very short in various cases.

Although the influence of the homecoming of discharged patients on the percentage of resistance staphylococci is in itself not of considerable importance, our material indicated that contact with the hospital sphere in various ways (hospitalization, visiting outpatient departments, visiting hospitalized friends, transfer from discharged patients) together formed the origin of about 60% of the resistant staphylococci found in the group of family members. The other 40% certainly do not represent any increase of the number of resistant staphylococci found in a normal population before antibiotic therapy was introduced. It seems possible however, that the importance of the hospital staphylococci present in the family members is greater than the percentage of their occurrence. The hospital staphylococci in general have proven to be really pathogenic, while a large part of the potentially pathogenic staphylococci which are carried by so many normal persons never seem to cause any infection. This would imply that the percentage of infections with resistant staphylococci might be higher than the percentage in which these strains are present.

Notwithstanding the fact that in Holland also the resistant flora in the population is influenced partly by contact with the hospital sphere, the figures for the resistance rate in the population examined by us are decidedly lower than those mentioned by Dowling et al. It seems possible that this is due to a difference in the way the medical treatment of the population is organized. In the Netherlands a large part of the medical care is given at the house of the patient or in the office of the general practitioners, outside of any contact with the hospital microflora. Neither the general practitioner himself nor his office nurse have any regular connection with the hospital sphere. The general practitioner hardly ever treats any of his own patients in hospital. If, however, the medical care is shifted more in the direction of help given by outpatient departments, as may happen in large metropolises, it seems possible that this more direct and more frequent contact with the hospital microflora might lead to an enforced infiltration of the population with hospital staphylococci. This may be especially so if there is no general insurance scheme which covers treatment at home by general practitioners. Also, health centers, if they are manned by a staff or by nurses who have regular contact with a hospital, might act in the same way. It is possible that in the Netherlands also there might be differences in this regard between the population of the larger cities and the rural areas. In this regard it seems worth while to mention that most patients of the University Hospital of the University of Leyden come from the city of Leyden, which in itself is only a rather small town of 120,000 inhabitants, and from the rural districts surrounding it. One can conceive the possibility that once a considerable increase of resistant staphylococci has taken place by infiltration of hospital staphylococci, antibiotic therapy in general practice also will lead to colonization of resistant micrococci from the surrounding microflora.

As a final conclusion, one could state that the fight against antibiotic resistance in staphylococci is primarily a question of epidemiological character, i. e., the interruption of the chains of infection of these micro-organisms in the hospital. As long as this is not possible in a really efficient way, the promoting effect of antibiotic therapy on colonization with resistant staphylococci in hospitalized patients should be curtailed by using these medicaments only on strict indication. In general practice as organized in Holland, the contact between hospital microflora and the general population seems

to be sufficiently small to preclude any considerable increase in resistance. However, in the larger cities and industrial centers, where patients are referred more easily and more intensively to outpatient departments or large dressing stations, the problem merits constant attention.

Summary

An examination was performed to investigate (a) the influence of antibiotic therapy on the frequency and the pattern of resistance in pathogenic staphylococci as present in the vestibulum nasi of 587 patients at the moment of discharge; (*b*) the fate of the resistant staphylococci after the patients were discharged, followed up in 61 patients, as compared with the fate of sensitive staphylococci, taken along from the hospital in 21 patients, and the course of the further carrier rate in 52 patients who left hospital without a pathogenic Staphylococcus in the vestibulum nasi; (*c*) the spread of these resistant hospital staphylococci in 455 family members and household contacts of 138 patients in a period of 6 to 12 months after discharge.

At the moment of discharge about 40% of the patients were carriers of a penicillin-resistant Staphylococcus; 30%, of a streptomycin-resistant strain; 25%, of a tetracycline-resistant one; 9%, of a chloramphenicol-resistant culture, and 2%, of an erythromycin-resistant strain.

Antibiotic therapy in the hospital promotes the colonization of resistant hospital staphylococci in the vestibulum nasi but is not a necessary factor.

The total pattern of resistance of the colonizing Staphylococcus is mainly decided by the pattern of resistance of the Staphylococcus strain circulating in the hospital at that moment and only partly by the type of antibiotic therapy. The colonization, however, will happen by preference by a strain resistant to the antibiotic therapy given at that moment.

Besides the influence of antibiotic therapy, there seems to be a private disposition of the patients, which also is of importance in deciding whether the patient will acquire a hospital Staphylococcus in his vestibulum nasi.

After discharge a large part of the hospital strains acquired by the patients gets lost. After 6-12 months the carrier rate for pathogenic staphylococci and the resistance rate for penicillin has become normal, while resistance against chloramphenicol has disappeared completely. The rate for streptomycin and tetracycline resistance at that moment, however, is still higher than normal.

The decrease in chloramphenicol resistance is based partly on loss of the resistant strains but also in a considerable part on loss of resistance, while the strain itself stays present in the patient. The decrease in resistance against the other antibiotics is, with a few exceptions for tetracycline resistance, due only to loss of the resistant strains.

Transfer of resistant strains from the vestibulum nasi of discharged patients occurs in 8% of the family members and household contacts and in 11% of the families of those patients discharged with with a resistant Staphylococcus. Figured on all discharged patients together, the percentages of transfer are 3% of the family members or household contacts and 4.5% of the families.

In about 60% of the resistant staphylococci in the family members the origin of the strain could be traced to direct or indirect contact with the hospital microflora (nospitalization, visit to outpatient departments, visit to hospitalized relations, transfer from discharged patients).

Antibiotic resistance in pathogenic staphylococci is mainly an epidemiologic problem.

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The Results of Five Hundred Percutaneous Renal Biopsies

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More than eight years have elapsed since the first percutaneous renal biopsy was carried out (Iversen and Brun [6]), and so far the results of about 1800 renal biopsy attempts have been published. Experience has now become so comprehensive that it is possible to form a broad impression of the nature and frequency of the complications in this procedure.

The aim of the present paper has been to examine the more than 500 renal biopsy attempts with any associated complications which have been carried out in Medical Department III of Kommunehospitalet throughout the period May, 1949, to January, 1958.

The literature to date contains a number of descriptions of complications in renal biopsy which are worth mentioning in detail.

Alwall [1] reported in 1952 that in 1944 he had had 1 death after renal biopsy in a series of 13 biopsies. The death occurred in a patient who went into shock after the biopsy and who was first treated 12 hours later. Neither during an ensuing decapsulation operation nor subsequently at autopsy could any hematoma be demonstrated, which must raise serious doubts whether the death should actually be ascribed to the renal biopsy. The author, in a later publication together with Erlanson and Tornberg,[2] has in fact considered the possibility that the death might have been due to a retrograde pyelography which was carried out at the same time. We share Alwall's latter opinion.

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Among 50 biopsy attempts, Parrish and Howe [11] have had one serious complication: renal biopsy (performed with a Turkel biopsy instrument) evoked a large retroperitoneal hematoma in a patient with hypertension. It was located, drained, and packed; the patient made an uneventful recovery. Howe [4] has stated later that the surgical intervention was possibly unnecessary.

Reubi,[12] in a series of biopsies (number not stated), saw one death, ascribed to renal biopsy:

> In a patient with bilateral hydronephrosis, chronic uremia and anemia a renal biopsy is carried out, apparently without complications. Prothrombin time and bleeding time are normal, while coagulation time and thrombocyte count are not stated. Roentgenologic examination of the colon using a barium enema is carried out on the following day, after which pain is experienced in the right renal region. The patient is found anuric that evening. Ureteric catheterization next day shows neither urine nor blood. Four days after the biopsy the right kidney is explored operatively and a partly clotted, moderate perirenal hematoma found, which is drained. The kidney is decapsulated. The patient dies the same evening in circulatory failure. Autopsy provides no explanation for the death. The site of the biopsy can just be seen, the hilum vessels and pelvis are not traumatized; both pelves contain urine.

In view of the clinical course, a potassium intoxication may be suggested as the immediate cause of death, but the article contains no data on this.

Ross and Ross [13] have observed one patient who developed a large retroperitoneal hematoma after renal biopsy, necessitating blood transfusion; the patient had malignant hypertension with uremia. The biopsy specimen showed severe amyloid infiltration of the glomeruli and blood vessels, includ-

ing a large artery from which the bleeding had probably occurred; there was no hematuria. The patient was discharged symptom-free 14 days after the biopsy.

Zelman [14] reports a case of bleeding after simultaneous liver and renal biopsy in a moribund patient, suffering from a severe acute glomerulonephritis with uremia following an upper respiratory infection together with a periodontal abscess. Bleeding, clotting, clot retraction, and prothrombin times are stated to have been within normal limits, but no thrombocyte count is mentioned, and capillary fragility was not determined. Scratchings on the surface of the liver were "deliberately produced before penetration of the liver was attempted." After the biopsies the patient gradually lapsed into coma and died about 10 hours later. Hemorrhage was not suspected from the clinical observations. At autopsy the abdominal cavity was found to be filled with 2 liters of fluid and clotted blood. Right perirenal hemorrhagic infiltration was present, possibly amounting to half a liter of blood. Hemorrhages were found subendocardially, in the stomach mucosa and renal pelves. The autopsy report suggests the diagnosis of an acute interstitial nephritis or a pyemic kidney. The author concludes that the bleeding in this case may have been caused by an increased capillary fragility, which he supposes existed prior to the biopsy as a result of the uremia.

Muehrcke, Kark, and Pirani,[9,10] in 1955, reported the complications in 100 renal biopsy attempts on 87 patients, kidney tissue being obtained in 96 of the attempts; microscopic hematuria was observed in all 96 instances. The only complications were the following two: gross hematuria in seven and pain in the loins in eight.*

* A paper by R. M. Kark, R. C. Muehreke, V. E. Pollak, C. L. Pirani, and J. H. Kiefer, "An Analysis of Five Hundred Percutaneous Renal Biopsies," (ARCH. INT. MED. 101:439, 1958) has appeared since completion of this paper. Their conclusions are in close accordance with our results.

Material

In all, 510 attempts have been carried out on 406 patients. Of the 67 patients who had more than one renal biopsy, 54 patients had two; 6 patients, three; 3 patients, four; 1 patient, five; 1 patient, six; 1 patient, seven, and finally, 1 patient, eleven biopsies.

Two techniques have mainly been employed throughout this period: from May 1949 to July 1954, biopsy was carried out with the patient in the sitting position; 267 renal biopsy attempts having been made by this method, while after July, 1954, we have placed the patient in the prone position with a sandbag under the abdomen, and 243 renal biopsy attempts have been carried out with this procedure. In all cases, the biopsies were carried out with the Iversen-Roholm cannula and syringe.[5] By means of the cannula, a cylinder of 1.5 mm. diameter and of varying length is cut from the kidney tissue. The cut tissue is retained in the needle during removal by a vacuum created by the special syringe.

As to the *effectivity* of these two procedures, we obtained satisfactory biopsy specimens in 106 of the 267 attempts in the sitting position (40%) and in 162 of the 243 attempts in the prone position (67%). The effectivity in both methods has risen with increasing practice.

The *patient material* comprised a variety of nephropathies, although it consisted predominantly of patients with acute anuria, diabetic nephropathy, glomerulonephritis and chronic pyelonephritis. Renal biopsy was carried out on 74 of the 276 patients admitted to the hemodialysis unit of the department during the period from January, 1954, to January, 1958, so that 27% of the patient material in this unit had renal biopsy carried out.

In the material, a total of 119 attempts at renal biopsy were made in cases of uremia (defined as a serum creatinine $\geqq$6.0 mg/100 ml. at the time of biopsy); 88 of these cases of uremia were acute; 31, chronic. With regard to the occurrence of hypertension in the patient material, the systolic pressure in 105 patients at the time of biopsy was higher than 160 mm. Hg and in a further 24 patients, $\geqq$200 mm. Hg.

Complications in Renal Biopsy Material

(*a*) *Microscopic Hematuria.*—The first two urine portions passed after each renal biopsy attempt were centrifuged and the sediment examined microscopically for erythrocytes. Microscopic hematuria is a natural sequel to kidney biopsy, although it does not appear to be obligatory.

The Frequency of Gross Hematuria by 510 Kidney Biopsy Attempts

	Gross Hematuria			
	Day of Biopsy		Following Day	
	Cases	%	Cases	%
All cases (510)	40	7.9	33	6.6
119 cases with uremia	12	10.1	10	8.4
365 cases without uremia	28	7.7	23	6.3
105 cases with systolic BP ≧ 160 mm. Hg	13	12.4	7	6.7
24 cases with systolic BP ≧ 200 mm. Hg	3	12.5	2	8.3

(*b*) *Gross Hematuria.*—Urine passed on the day of the biopsy and the following day was collected separately and observed for gross hematuria and presence of blood clots. Attacks of renal colic were noted.

Gross hematuria on the day of biopsy was found after 40 biopsies (7.9%). In 33 biopsies the hematuria was still present on the following day (6.6%) (Table).

Blood clots in the urine were observed 19 times, and renal colic presumably due to passage of clots was noted 5 times.

(*c*) *Uncontrollable Hemorrhage.*—Uncontrolled hemorrhage was not seen after renal biopsy except in one patient, who was intentionally heparinized 24 hours after biopsy for hemodialysis (see below).

(*d*) *Retroperitoneal Hematoma.*—A moderate retroperitoneal hematoma was seen in one case, but surgical intervention was not considered necessary, and it had no influence on the further course of the case.

Biopsy 275.—A 29-year-old woman admitted in very bad condition with severe septicemia (Staphylococcus aureus) and widespread, bilateral infiltrations of the lungs. Urine volume decreased gradually to 50 ml/24 hours. NPN rose. Thrombocytes 71,000 per microliter. Bleeding and clotting time moderately increased. As the differential diagnosis between acute glomerulonephritis and ischemic anuria was considered important on account of a possible treatment with hemodialysis, a renal biopsy was performed on the eighth day of anuria. The biopsy was followed by drop in blood pressure from 135 to 70 mm. Hg and clinical signs and symptoms of shock, which subsided only after 2 pt. (500 cc.) of blood was given. A tender mass was palpated in the right kidney region. Gross hematuria continued, and several transfusions were necessary in the following days. Five days after the biopsy (30th day of disease) the patient suddenly died in convulsions.

Postmortem examination showed severe acute ulcerative endocarditis of tricuspid valve, myocarditis, and multiple abscesses of lungs and kidneys. Brain: disseminated acute pyemic abscesses and edema. Kidneys: The right kidney was surrounded by a zone of coagulated blood, nowhere exceeding 5 cm. No subcapsular bleeding; no laceration of the tissue. The right renal pelvis and right ureter contained coagulated blood. Histological diagnosis: pyemic kidney.

(*e*) *Blood Transfusion.*—Blood transfusions have been given on 11 occasions in connection with renal biopsy attempts (2.2%). In view of this, we have always carried out blood-group determinations and had compatible blood ready in each renal biopsy attempt.

(*f*) *Syncope.*—We have observed a fall in blood pressure of brief duration in some few patients when placed in the prone position. The fall in blood pressure is presumably due to a reduction in the venous return to the heart. Lying for longer periods in the prone position must therefore be advised against if the patients cannot stand this.

(*g*) *Kidney Function Before and After Biopsy.*—We have determined the endogenous 24-hour creatinine clearance before and after the biopsy in 173 unselected renal biopsy attempts, as an indication of the glomerular filtration. A comparison of the creatinine clearance before and after the biopsy shows that in 139 attempts (80%) the clearance was unchanged or higher after the biopsy; only in 34 attempts (20%) had the clearance fallen by more than 10% of the initial value. In only two cases was a marked fall observed in the clearance after biopsy (defined as a fall of more than 30% of the initial value), in both cases due to transient blockage of the ureter by blood clots. As soon as the clots were removed the clearance reached the initial value.

It may thus be concluded that the creatinine clearance is not found to be affected by the renal biopsy procedure as such.

(*h*) *Renal Biopsy Prior to Hemodialysis.* As in our opinion renal biopsy has great diagnostic value in acute renal insufficiency, and therefore also as a method of examination prior to hemodialysis, it is of significance to investigate the risk associated with renal biopsy attempts when they are carried out prior to hemodialysis, during which, of course the patients are heparinized.

As mentioned, 74 renal biopsy attempts have been carried out in our dialysis unit; of these, 19 were made prior to dialysis (one day prior to dialysis in four patients, two days prior in four patients, three days prior in three patients, four days prior in two patients, five days prior in one patient, and six days prior in five patients). In 18 patients the course of the biopsy was without complications, also in connection with the subsequent hemodialysis; the case of the 1 patient who developed a serious complication in association with the subsequent dialysis is described in the following paragraph.

Biopsy 343.—A 53-year-old woman was admitted with high fever, jaundice, anemia, drowsiness, uremia, and increasing oliguria. Septicemia (pneumococcus Type 14) and a lobar pneumonia in the lower lobe of the right lung were found. She was dialyzed twice because of uremia and elevated serum potassium. A renal biopsy was done, as no explanation of anuria could be found in the clinical and laboratory data. No untoward effect of the biopsy was seen until 24 hours later, when a third dialysis was inevitable, owing to high and rising serum potassium values (7.6 mEq. per liter). After three hours of dialysis a steady stream of fresh blood started to flow from the urethra, and rapid constant infusion of blood under pressure was necessary to prevent the patient from going into shock. Finally a right nephrectomy was carried out, during which the patient was in shock for 10-15 minutes. Fifty transfusions of 500 ml. of blood were necessary before the bleeding could be controlled. The removed kidney showed bleeding in pelvis and peripelvic fat, and by injection an open connection between an artery and the renal pelvis was found. The postoperative course was uneventful, and the patient gradually regained kidney function and recovered. She was discharged with an endogenous creatinine clearance of about 50% of normal.

(*i*) *Lesion of the Gallbladder.*—In a single patient in uremic coma, a lesion of the gallbladder was observed, which however had no influence on the course of the disease. Autopsy showed chronic pyelonephritis, cerebral edema, cerebral softening in the pons. A moderate hematoma was found in the right perirenal tissue; no tear of or bleeding in the kidney tissue or pelvis. The gallbladder was of normal size and contained some coagulated blood and in its wall a small hematoma was found, 10 mm. in diameter; 10-20 ml. of coagulated blood was found below the right diaphragm. No bile was found in the peritoneal cavity.

(*j*) *Pain in the Loins.*—In 37 cases among the 510 biopsy attempts (7%) the patients stated that they had pain in the loins after the biopsy. The pain, usually localized to the site of the biopsy, was of moderate intensity and only required the use of analgetics in a small number of cases. In some few cases (5) the pain was of a colic-like nature, presumably due to the passage of clots.

(*k*) *Rise in Temperature After Biopsy.* We have also investigated the frequency of fever after renal biopsy, with particular attention to chronic pyelonephritis, in order to examine whether the inflammation can be activated or disseminated by the renal biopsy.

Temperature rises to above 38 C (100.4 F) were observed in two cases (3.2%) among 62 attempts at renal biopsy on patients with chronic pyelonephritis, while in the remaining patient group (which contained all kidney diseases with the exception of pyelonephritis) a temperature rise was observed in 15 cases out of 422 (3.6%). Rise in temperature is thus a rare sequel to biopsy, and biopsy in cases of pyelonephritis does not raise the frequency; there is nothing to suggest that pyelonephritis is activated by carrying out renal biopsy.

(*l*) *Autopsy Observations.*—The autopsy records were examined for 96 patients on whom renal biopsy had been carried out within six months of death. In spite of

careful search it was only possible to demonstrate the site of biopsy in 23 of these, usually as a circular defect in the surface of 2 mm. in diameter. In no case was laceration of the kidney tissue found. In 24 patients a minor hematoma was found in the fat capsule of the kidney, usually corresponding to 10-20 ml. of blood.

(m) Gross Hematuria in Uremia and Hypertension.—It has been maintained by a number of authors (Lich [7]; Lusted, Mortimore, and Hopper [8]; Muehrcke, Kark, and Pirani,[9,10] and Zelman [14]) that uremia must be considered a counterindication for renal biopsy on account of the hemorrhagic diathesis which can be associated with the condition. We have therefore investigated the frequency of gross hematuria among our cases of uremia compared with the remaining material of nonuremics. Patients with hypertension have been investigated in this respect, as this is also likewise claimed to increase the risk of bleeding (de Wardener and Hutt [3]).

Biopsy attempts were made on 119 patients with uremia; the material contains 365 attempts on nonuremics; the serum creatinine of the remaining 26 patients were not estimated. Gross hematuria on the day of biopsy was found in 12 of 119 attempts on patients with uremia (10.1%), while among the nonuremics 28 (7.7%) were found who had gross hematuria on the day of biopsy.

In the material there were 105 attempts in which the systolic blood pressure was above 160 mm. Hg just prior to the renal biopsy and 345 attempts in which the systolic blood pressure was equal to or less than 160 mm. Hg. Among the patients whose blood pressure was above 160 mm. Hg, there were 13 with gross hematuria on the day of biopsy (12.4%); among 345 patients with a blood pressure equal to or less than 160 mm. Hg, there were 27 with gross hematuria on the day of biopsy (7.8%). Among 24 patients with a blood pressure equal to or more than 200 mm. Hg, 3 patients had hematuria on the day of biopsy (Table).

In patients with arterial hypertension and patients with uremia, the frequency of gross hematuria after biopsy did not deviate significantly from the frequency of hematuria in the remaining patients.

No deaths have been observed in our material which might be ascribed to renal biopsy. It is therefore our opinion that on diagnostic, prognostic, therapeutic, and scientific grounds it is reasonable and safe to continue carrying out renal biopsies. By way of precaution it is advisable to perform renal biopsy on hospitalized patients only. However, only those departments particularly interested, and which are in the position to acquire a reasonable experience, should take up this procedure.

As there are only about 1800 cases of renal biopsy reported in the literature to date, it is still too early to express the risk in renal biopsy in figures and to compare this with the figures in the case of liver biopsy.

Summary

Five hundred ten attempts at percutaneous renal biopsy were made on 406 patients in the period from May, 1949, to January, 1958. The 510 attempts resulted in 268 renal biopsies which were suitable for histological interpretation. In the period from May, 1949, to July, 1954, the biopsy was carried out with the patient in the sitting position; from July, 1954, the patient has been placed in the prone position with a sandbag under the abdomen.

The following complications were observed: Gross hematuria on the day of biopsy was observed in 7.9%; hematuria, persisting beyond the day of biopsy, was observed in 6.6%. Blood clots in the urine were found in 19 cases, and ureter colic, in 5 cases. A moderate retroperitoneal hematoma was seen in one case, but surgical intervention was not considered necessary. In 2.2% of the attempts blood transfusion was given following the attempt; in view of this, blood-group determination should

always be carried out and compatible blood should be available on each attempt. In by far the majority of cases, the kidney function—expressed by endogenous 24-hour creatinine clearance—was unaffected by the renal biopsy; only in two cases was the renal function briefly reduced after the renal biopsy, in both cases due to ureter obstruction by blood clots. After removal of the clots the creatinine clearance quickly reached the initial value. Hemodialysis may be carried out after renal biopsy, but one should wait a few days after the biopsy before subjecting the patients to the heparinization necessary to the dialysis. Pain in the loins after biopsy attempt was reported by 7% of the patients. Temperature rise after renal biopsy is rare (3.6%), and renal biopsy in cases of chronic pyelonephritis does not raise the frequency. Statistical analysis shows that the occurrence of macroscopic hematuria after renal biopsy in patients with uremia and hypertension has no demonstrably higher frequency than in patients without these symptoms.

No deaths were observed in our material as a consequence of renal biopsy. As so far only about 1800 cases of attempts at renal biopsy have been published, it is too early as yet to compare the risks in liver biopsy and renal biopsy.

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The Clinical Manifestations of Gastroileal Anastomosis

With Particular Reference to Potassium Deficiency

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The consequences of an inadvertent gastroileostomy are discouraging to all concerned. Although the wasting and physical deterioration which such patients usually experience are impressive, fortunately the condition can be corrected surgically and seldom has proved fatal. However, because death is the inevitable result of gastroileostomy if the presence of the stoma goes unrecognized and because the clinical picture resulting from this surgical error at times may be atypical, it is well for all physicians to be acquainted not only with the usual clinical manifestations but also with the clinical variants.

As nearly as can be determined, surgical correction of a gastroileal anastomosis was first carried out at the Mayo Clinic in 1912 by Judd,* and repair in another case was performed only seven weeks later by W. J. Mayo (Case 2 reported by Smith and Rivers). Since that time repairs have been done in 30 additional cases at the clinic, and we have found reference to 52 others in the literature, which make a total of 84 to September, 1957.[1-5,8,12-14,17-21,24-26,28,31,33-36,38,39,43-49,51] Thus, such cases cannot be considered rarities any longer, and, indeed, as others have observed, it is likely that a number of cases are encountered but not reported each year. In this connection it is worth noting that no case has yet been reported in which both the gastroileostomy and the disconnection of this anastomosis at a later date have been done by the same surgeon. Smith and Walters summarized experience at the clinic with 25 cases prior to 1951. In recent years these cases have been encountered at the clinic at the average rate of one each year. Five recent cases are described briefly herein to illustrate certain of the clinical features of gastroileal anastomosis. The most recent patient (Case 1) presented with the clinical picture of marked potassium deficit; the history otherwise is more or less typical of most patients with a gastroileal stoma.

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* The clinic records of Judd's patient have been reviewed, and the account is as indicated in the letter published by Mercur.

Report of Cases

CASE 1.—This 40-year-old white man came to the clinic Nov. 14, 1955, and was hospitalized immediately. He complained of diarrhea and weakness which began on Aug. 13, 1955. He had been well until 1945, when recurrent spells of epigastric pain-food-ease had begun and a duodenal ulcer had been found roentgenologically. For the next 10 years recurrences had continued and he had experienced progressively more difficulty. He had begun to vomit and had lost 30 lb. in the three months prior to subtotal gastrectomy, which had been performed elsewhere on Aug. 6, 1955. At that time an obstructing duodenal ulcer was said to have been found. The patient had done well for one week after operation, when he began to note severe lienteric diarrhea, weakness, further loss of weight (20 lb.), and slight abdominal cramps. Six weeks after operation occasional vomiting began, and on a few occasions this had been fecal in character.

On examination at the clinic the patient's oral temperature was 95 F. The pulse rate was 42 beats per minute, with apparently regular rhythm. The blood pressure was 80 mm. of mercury systolic, 50 diastolic. The patient was markedly

dehydrated and wasted, and he appeared depressed. He was too weak to dress and undress himself without help. The tendon reflexes were absent. The Chvostek sign was negative. Abdominal examination was negative except for a well-healed abdominal scar. The patient interrupted physical examination on several occasions to defecate. He weighed 101 lb.

Laboratory studies revealed the following values: blood hemoglobin 12.2 gm. per 100 ml., erythrocytes 3,770,000 per cubic millimeter, and leukocytes 4400. The sulfobromophthalein (Bromsulphalein) test of liver function showed no retention of dye at the end of one hour, and values for serum bilirubin were normal. The prothrombin time was 20 seconds. The concentration of fasting blood sugar was 90 mg. per 100 ml. The blood urea measured 10 mg. per 100 ml. Values for plasma chlorides were 108 mEq. per liter and for carbon dioxide-combining power, 15 mEq. per liter. Values for serum albumin and globulin were 3.1 and 1.3 gm. per 100 ml., respectively. The initial serum potassium level was 1.8 mEq. per liter, and the serum sodium measured 135 mEq. per liter. Stools passed at the time of physical examination were liquid and contained undigested particles of food. Microscopic examination of the stools showed excess fat and meat fibers. Roentgenograms of the chest were negative except for old healed fractures of the left sixth and seventh ribs. Roentgenologic studies of the stomach were interpreted as showing gastrojejunocolic fistula in the region of the anastomosis. Barium study of the colon appeared to show evidence of a jejunocolic fistula communicating with the transverse colon; the stomach was not filled on that examination. The initial electrocardiogram reflected the changes of potassium deficiency (Fig. 1).

A gastroileal stoma was suspected. The patient was given a diet low in residue and high in calories, protein, carbohydrate, and potassium and was given supplemental potassium in large doses in the form of beef broth, tomato juice, bouillon and an elixir containing potassium gluconate by mouth, as well as potassium chloride by vein. After a week of such therapy the concentration of potassium in the serum was normal, although only

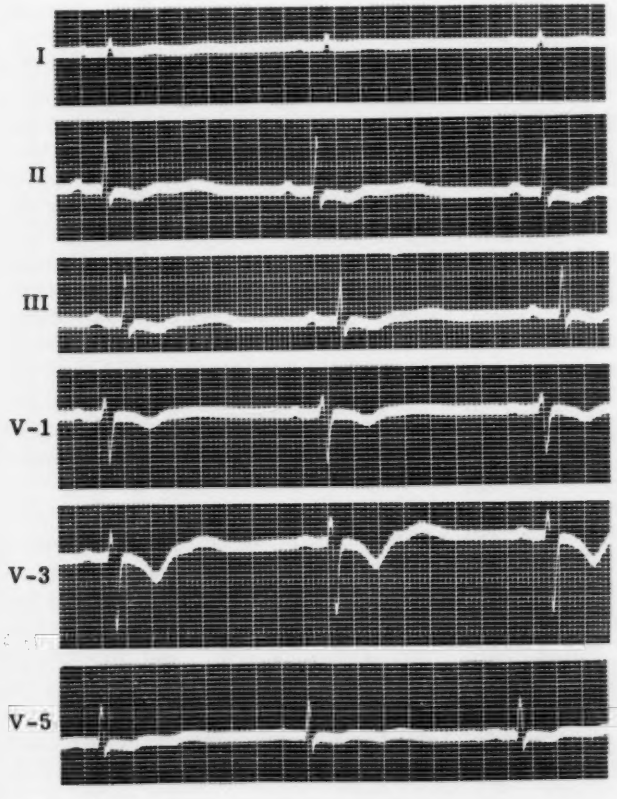

Fig. 1 (Case 1).—Electrocardiogram exhibiting changes characteristic of potassium depletion. Note the bradycardia, prolongation of the Q-T interval beyond that expected for the rate, inversion of T waves and prominent U waves. After a week of intensive oral and parenteral administration of potassium the value for serum potassium was normal but the electrocardiographic pattern was only slightly improved. This lag phenomenon and the lack of correlation at times between the concentration of serum potassium and the electrocardiographic pattern have been observed by others.[6,35,41]

Data on Potassium in Case 1

Date	Serum Potassium, mEq/L.	Potassium Therapy, mEq.* Potassium Gluconate P. O.	Potassium Chloride, I. V.	Total
11-15-55	1.8			
11-16-55		30+	40	70+
11-17-55		30+	40	70+
11-18-55	1.6	80	40	120
11-19-55		150	40	190
11-20-55		300	140	440
11-21-55	3.3	240	136	376
11-22-55		360	64	424
11-23-55	5.4	120	120	240
Total		1,310+	620	1,930+
11-25-55	Operation			
11-26-55	4.3			
11-30-55	2.7			

* Potassium administered in addition to that taken in the diet.

slight improvement was evident in the electrocardiogram (Table).

At operation, on Nov. 25, 1955, the presence of a gastroileal anastomosis was confirmed and peptic ulcers were found in the ileum. About half of the stomach had been removed previously, and the anastomosis had been made approximately 12 to 14 in. (30.5 to 35.6 cm.) proximal to the ileocecal valve. There was no colic fistula. The ileum was disconnected by resecting a segment, which was much inflamed and which contained several small ulcers; ileal continuity was reestablished by an end-to-end ileoileostomy. Further resection of the stomach was carried out. Gastrointestinal continuity was reestablished by a Hofmeister operation. Pathologic examination of the resected specimen showed 12 cm. of stomach and 10 cm. of attached ileum with an end-to-side gastroileal anastomosis. Chronic gastritis with hemorrhagic gastroileitis and multiple superficial mucosal peptic ileal ulcers measuring from 3 mm. to 1 cm. in diameter were present.

Postoperatively moderate hypokalemia and dumping symptoms developed; these had decreased two months later. Shortly after leaving the hospital, the patient was aware of numbness in the hands and difficulty in walking. Neurologic examination revealed peripheral neuropathy (mononeuritis multiplex), considered to be the result of nutritional deficiency. Two months after operation the patient had gained 30 lb. and looked and acted like a different person.

Comment.—Initially the patient complained of severe diarrhea which consisted of 5 to 20 stools per 24 hours, with 2 or 3 of them at night. These stools were bulky and frothy and contained undigested food, including meat. The patient had become progressively weaker until he was almost prostrate at the time of admission to the hospital, and he had had some cramping in his legs. Although a gastroileal anastomosis was considered to be the most likely lesion, the possibility of a gastrojejunocolic fistula was also considered.

The clinical picture of low concentrations of potassium in the tissue cells and serum was unmistakable in Case 1. Hypokalemia following gastroileostomy has been reported on only a few occasions.[4,12,28,49] A case similar to our Case 1 was reported by Brine and Fraser, in which the serum potassium at one point fell to the remarkable level of only 0.7 mEq. per liter. Since on admission to the hospital our patient was acidotic (reduction of carbon dioxide-combining power of the plasma almost to 50% of normal), it is likely that the intracellular stores of potassium were even considerably lower than was reflected by the low concentration of potassium in the serum (1.8 mEq. per liter), for acidosis may result in elevations of as much as 3 mEq. per liter in serum potassium concentrations.[7] Moreover, in view of the low concentration of serum potassium and the inferred low intracellular stores of potassium, the marked loss of weight, with attendant shrinkage of total potassium capacity of the body, makes it evident that the total body content of potassium also was markedly reduced. The electrocardiographic evidence and the difficulty encountered in replacing the potassium stores of the body also indicated the presence of severe depletion of potassium in this case. It seems likely that the potassium which was taken orally prior to disconnection of the gastroileal anastomosis played little part in replacing the potassium stores of the body, since this potassium bypassed most of the intestinal absorptive surface. Potassium deficit and hypokalemia resulting primarily from increased fecal excretion of potassium have been reported in other conditions associated with severe and prolonged diarrhea, including infantile diar-

rhea,[16] chronic ulcerative colitis,[32] nontropical sprue,[9-11,23,32,40] long-standing functional diarrhea,[37] chronic laxative abuse,[41,42] gastrojejunocolic fistula,[27] and Whipple's disease.[22,30] One must be alert to the possibility of potassium depletion in such cases and take appropriate corrective measures when necessary, delaying any indicated surgical procedure until potassium stores of the body have been repleted.

The following four cases illustrate other clinical features which may be encountered when a gastroileal anastomosis was effected inadvertently.

CASE 2.—A 62-year-old white farmer first came to the clinic Dec. 3, 1951. He had been troubled for 40 years with epigastric burning and gnawing distress two or three hours after eating for a week or so spring and fall; relief was obtained from food or alkali. The symptoms had become progressively more troublesome through the years, eventuating in gastroenterostomy for duodenal ulcer elsewhere in June, 1950. The patient had done fairly well for three months after operation, but then the symptoms of ulcer had recurred as before, with posterior reference of pain and increasing tempo. He had experienced considerable night pain and for some weeks had taken alkali every hour and one-half day and night for relief. His weight prior to June, 1950, had been 130 lb., and he had lost 20 lb. since that time. He had not been troubled with nausea, vomiting, melena or diarrhea; in fact, he had been slightly constipated for some years, without change. His appetite had been poor since the operation.

On examination the patient was 65 in. tall and weighed 107 lb. Moderate epigastric and left subcostal tenderness and voluntary guarding of the upper part of the abdomen were evident, but the examination was not remarkable otherwise.

Gastric aspiration in the hospital yielded 1700 ml. of retained material on one occasion. Roentgenologic examination of the stomach revealed a nonfunctioning gastroenteric stoma, duodenal ulcer with moderate gastric obstruction, and possibly a small ulcerating gastric lesion off the lesser curvature on the posterior wall above the angle.

At operation, on Dec. 10, 1951, a gastroileal anastomosis was discovered approximately 24 in. (61 cm.) above the ileocecal valve; the gastroileal stoma had become narrowed to about 1 cm. in diameter. A reactivated perforating duodenal ulcer formed a mass about 2.5 cm. in diameter with a crater 1.5 cm. in diameter. The duodenal ulcer had perforated into the undersurface of the liver and the falciform ligament of the liver. No gastroileal ulcer was visible, although the anastomotic area was inflamed and the proximal limb of the ileum was dilated and thickened. The gastroileal anastomosis was disconnected, the opening in the ileum was closed, and partial gastrectomy and partial duodenectomy with removal of the ulcer and anterior Polya anastomosis were carried out. Pathologic examination of the specimen removed revealed subacute duodenitis with a portion of a penetrating chronic duodenal ulcer 2.5 cm. in diameter. Examination of the stomach showed chronic gastritis with multiple small erosions and a chronic pyloric ulcer 1 cm. in diameter on the lesser curvature. Hemorrhagic gastroileitis was noted, with marked fibrous stenosis of the stomach.

Comment.—In Case 2 it seems likely that the gastroileal stoma had become nonfunctioning shortly after it had been established and had remained so, inasmuch as the patient had not been troubled with lienteric diarrhea or other evidences of malabsorption. His symptoms were clearly the result of pyloric ulcer and reactivated duodenal ulcer, with eventual pyloroduodenal obstruction.

CASE 3.—A 42-year-old white farmer came to the clinic Jan. 7, 1952, complaining chiefly of fecal vomiting and loss of 40 lb. in the preceding three months. For 25 years he had experienced intermittent epigastric pain between meals, which was relieved by eating. Roentgenologic examination in 1931 was said to have shown gastric ulcer. After a 9-year period of remission he had experienced recurrent symptoms of ulcer for the 11 years prior to 1951, when rather frequent vomiting and also hematemesis occurred. On Oct. 31, 1951, gastroenterostomy had been performed elsewhere. Ten days after operation, on his resuming ingestion of solid food, the patient began to have fecal belching and vomiting and to pass two small gray stools each day. These symptoms had continued up to the time of examination at the clinic. The patient also complained that the food seemed to fall down to the lower part of the abdomen shortly after eating. The stools had been mushy and at times watery and occasionally had forced him to get up at night. Roentgenologic studies carried out elsewhere were said to have shown a gastrojejunocolic fistula.

Physical examination at the clinic disclosed a slender man who was active and did not appear ill. No significant abnormalities were detected. His height was 67 in. and weight was 119 lb.

The patient was not anemic. The concentration of serum albumin was 3.7 gm. per 100 ml., and of globulin, 1.6 gm. The prothrombin time was normal. Roentgenologic study of the colon revealed

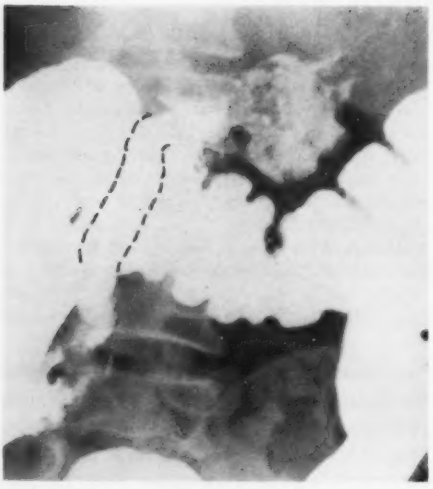

Fig. 2 (Case 3).—The colon before operation at the clinic, showing prompt retrograde passage of barium into the stomach via the short segment of terminal ileum (dotted lines) previously anastomosed to the stomach.

a gastroileal stoma when the barium entered the terminal ileum in retrograde fashion and shortly thereafter passed into the stomach (Fig. 2).

At operation, on Jan. 15, 1952, a gastroileal anastomosis of the stomach was found about 12 in. (30.5 cm.) above the ileocecal valve. The anastomosis lay on the anterior surface of the pyloric antrum. The duodenum did not appear to be scarred, but a mass in the region of the pylorus proved to be a gastric ulcer. The gastroileal anastomosis was disconnected, and the defect in the ileum, sutured transversely. Approximately the lower three-fourths of the stomach was removed, and gastrointestinal continuity was reestablished by means of a Hofmeister type of gastrojejunostomy. Pathologic examination revealed chronic gastritis, duodenitis, and hemorrhagic ileitis. There was also a chronic inflammatory peptic ulcer 5 mm. in diameter on the lesser curvature of the stomach 2 cm. above the pyloric ring. The patient's postoperative convalescence was uneventful.

Comment—The clinical picture in Case 3 was characteristic of a gastroileal stoma: steatorrheal diarrhea, fecal belching, and fecal vomiting developed when the patient resumed eating solid foods 10 days following gastroenterostomy for duodenal ulcer. In addition, significant loss of weight had occurred after the short-circuiting operation. That the patient had not experienced severer diarrhea and evidences of malabsorption was doubtless attributable to the passage of a fair amount of the ingested food through the pylorus rather than through the gastroileal stoma.

Case 4.—A 52-year-old white man came to the clinic Aug. 5, 1952, complaining of diarrhea for the preceding month and edema of the legs for two months. In 1927, after a year of burning pain in the epigastrium an hour postprandially with relief by milk or food, the patient had undergone gastroenterostomy elsewhere. In the three weeks following that operation he had had three other operations because of malfunctioning of the gastroenteric stoma; apparently the first anastomosis had been taken down and two others established. The patient had been seriously ill after the last of these operations, having what was said to be peritonitis, and he had remained in the hospital for a month. He had improved and, except for six weeks of matinal vomiting in 1932 and two weeks of watery diarrhea and abdominal cramps in 1938, had been well until 1949, when he had become weak and tired and had received liver extract because of anemia. In November, 1951, his tongue became sore and remained so. In March, 1952, an incisional hernia had been repaired. In June, 1952, he had noticed swelling of the feet and legs and had lost appetite and strength. In July, watery diarrhea had begun with six to eight loose stools each day which contained undigested meat scraps and other food particles; he had been forced to get up at night to move his bowels at times. He also had experienced some paresthesia and cramping in his hands since onset of the diarrhea.

On examination the patient appeared markedly undernourished. The tongue was moderately reddened. There was marked pitting edema to the knees. He was 70 in. tall and weighed 127 lb.

Routine blood cell counts were normal, but the peripheral blood smear showed a borderline macrocytosis with mild hypochromasia. The serum albumin measured 2.9 gm. per 100 ml., and the globulin, 1.8 gm. The value for serum calcium was 8.4 mg. per 100 ml. Histamine-fast achlorhydria was demonstrated. Analysis of a 48-hour collection of stools with the patient taking a 100 gm. fat diet disclosed that the average daily fecal excretion of fat was 32 gm. and of nitrogen, 4.4 gm. An oral glucose tolerance test yielded a flat curve. Roentgenologic studies of the stomach disclosed a rapidly emptying gastroenteric anastomosis with patent pylorus, duodenal ulcer, and loops of jejunum matted together in the region of the stoma. Roentgenologic studies of the colon and terminal ileum gave negative results. Those of the small intestine revealed that both the pylorus and the gastroenteric stoma were patent and apparently emptying normally. The deformity

of a duodenal ulcer was noted again. The proximal limb of the gastroenteric anastomosis was felt to be a blind one. The distal portion of the duodenum and the upper jejunal loops were matted together, and what appeared to be a gastrojejunal fistula was distal to the gastroenteric anastomosis. Other enteroenteric connections could not be excluded.

After three weeks of intensive medical therapy, exploratory operation was performed on Sept. 4, 1952, at which time evidence of three previous gastroenterostomies was found: One in the jejunum had been disconnected previously, and another had been made proximal to it. In addition, a gastroileal anastomosis had been established between the upper part of the ileum and anterior wall of the stomach. There were many adhesions in the abdomen, and the transverse colon was adherent to the area of the incision as well as to an upper jejunal loop, probably the result of a healed jejunal ulcer. A jejunocolic fistula about 1 cm. in diameter was present. The obsolete and malfunctioning gastrojejunal and gastroileal anastomoses were disconnected, and the fistulous opening in the colon was closed. Portions of the ileum and of the jejunum were resected and subtotal gastrectomy and partial duodenectomy were performed with a Hofmeister type of anastomosis.

Following the corrective operation the patient made slow progress and continued to complain of paresthesia and some diarrhea. However, he ate well and improved steadily in the ensuing months.

Comment.—Case 4 has been included primarily to emphasize the point that the clinical picture of patients after gastroileostomy may sometimes be atypical and complicated. In Case 4 it was not possible to distinguish clearly those symptoms which were solely the result of the previous gastroileostomy. It seems likely that the lienteric diarrhea present for two months prior to the patient's coming to the clinic had resulted from the jejunocolic fistula. The stormy postoperative course following his fourth operation in three weeks in 1928 was perhaps partly a reflection of the gastroileal stoma. This anastomosis probably became malfunctioning at that time and had remained so through the years. This case seems to be unique in that borderline macrocytosis was present. As Brine and Fraser observed, megaloblastic anemia has not been reported in any patient with a gastroileal anastomosis. A possible explanation is that patients with severe diarrhea and intestinal malabsorption come to operation and repair of the gastroileal stoma before sufficient time has elapsed to deplete the stores of erythrocyte maturation factor in the body.

CASE 5.—A 54-year-old white man came to the clinic on Feb. 5, 1954, complaining of lienteric diarrhea for the preceding two months. Because of intractable duodenal ulcer he had undergone subtotal gastrectomy June 29, 1953, elsewhere. The immediate postoperative course had been uneventful, and he had done well for six months thereafter. He then had noted the gradual onset of diarrhea, abdominal discomfort, belching, bloating, and loss of weight, as well as matinal nausea. His appetite had remained good. For about two months prior to coming to the clinic, he had observed spinach and other food remnants in the stools three or four hours after having eaten them. He had lost 50 lb. in the eight months prior to examination. Associated with the diarrhea he had had paraumbilical aching between meals and occasionally at night; this had been relieved by eating. Roentgenologic examination had revealed evidence of a gastroileal stoma.

On examination at the clinic the patient appeared cadaverous. There was a ventral incisional hernia in the left upper rectus incision. He was 71 in. tall and weighed 117 lb.

Routine laboratory studies gave normal results. The concentration of serum albumin was 3.4 gm. per 100 ml. and of globulin, 1.9 gm. The value for serum potassium was 3.9 mEq. per liter. Roentgenologic examination of the stomach revealed evidence of a previous partial gastric resection with anastomosis between the stomach and the ileum about 3 ft. (91.4 cm.) from the ileocecal valve.

At operation, on Feb. 11, 1954, the presence of a gastroileal stoma was confirmed. Approximately the distal 60% of the stomach had previously been removed and an anterior von Eiselberg type of anastomosis performed, with the stoma placed in the ileum about 2 ft. (61 cm.) above the cecum. There was no evidence of ileal ulceration. The anastomosis was disconnected, and the opening in the ileum, closed transversely. Another 10% of the stomach was resected, and a Hofmeister anastomosis with the jejunum was established immediately distal to the ligament of Treitz. No other abnormalities were found on abdominal exploration. The pathologic report on the resected stomach was mild chronic gastritis. The patient's postoperative convalescence was normal.

Comment.—Mild hypokalemia was present in this case, again, as in Case 1, presumably the result of the intestinal short-circuiting previously established. The

symptom-free interval of six months following the gastroileostomy is noteworthy in this case, especially in view of the fact that subtotal gastrectomy had been carried out at the same time. Under these circumstances the symptoms referable to a gastroileal stoma usually begin when the patient resumes eating solid food in the immediate postoperative period.

Clinical Features

Common Symptoms.—The symptoms of those with gastroileal stoma were admirably described by Rivers and Wilbur [39] and by Smith and associates.[45,46] *A gastroileal stoma should be strongly suspected in any patient presenting with the combination of marked and progressive loss of weight and lienteric diarrhea beginning within a week or two of an operation for peptic ulcer.* Most patients have lost 20 to 50 lb. or more by the time the gastroileal stoma is suspected and repaired, but the appetite has usually remained good. Although loss of weight is the most frequently encountered symptom of a gastroileal stoma, the most distinctive feature is the onset of lienteric diarrhea a week after performance of an abdominal operation for peptic ulcer—that is, coincident with resumption of eating solid food after operation, for when the gastroileal stoma has been the sole or major exit for food from the stomach, most of the small intestinal absorptive surface has been bypassed. Other commonly encountered symptoms are belching and vomiting, which assume more diagnostic significance when they are of fecal character, as not uncommonly occurs. The emesis may be of gastric-retention type when the gastroileal stoma becomes malfunctioning and the pylorus is also obstructed or pyloroduodenal continuity has been disrupted, as when gastroileostomy was part of subtotal gastrectomy. Emesis may be hemorrhagic when a gastroileal ulcer or ulcer of the stomach or duodenum has become complicated by bleeding.

Abdominal Pain.—Sometimes abdominal pain is associated with these symptoms. This pain usually stems from a gastroileal ulcer or a persistent or recurrent ulcer of the duodenum or stomach. The pain of gastroileal ulceration is more or less typical of that associated with duodenal or gastric ulcer, except that it is generally felt somewhat lower in the abdomen. Such pain usually does not begin for some weeks or months after operation. Apparently gastroileitis also may cause pain, which is frequently of crampy character.

Variation in Time of Onset of Symptoms. Although the symptoms which result from a gastroileostomy most commonly begin within a week or two after operation and are most characteristic when they do occur at that time, occasionally a gastroileal stoma is tolerated rather well for extended periods—sometimes even for several decades; such patients may not lose weight or have diarrhea. When this situation obtains, gastroileostomy has not been combined with subtotal gastrectomy and much, if not most, of the food entering the stomach passes through the pylorus and traverses the small intestine normally. The symptoms of recurrent duodenal or gastric ulcer may continue through the years. If, later, pyloroduodenal obstruction occurs, the gastroileal stoma may function more, with consequent development of the characteristic symptoms described. If, then, the gastroileal stoma also becomes obstructed, emesis of retention type occurs. When partial gastrectomy and gastroileostomy have been performed at the same time, the characteristic symptoms due to gastroileostomy usually begin in the immediate postoperative period, although even under these circumstances in a few cases the symptoms have not begun for several months, as in Case 5.

Fecal Changes.—When the gastroileal stoma is functioning, food passes quickly from the stomach into the colon and appears undigested in the stools. The transit time of food and ingested carmine in our Case 1 was about two hours. The distance of the gastroileal anastomosis from the ileocecal valve is a factor which probably influences

to some extent the rapidity with which food appears in the feces. The retrograde passage of material from colon to stomach has accounted for the unusual complaint of tasting soap after the administration of a soapsuds enema in one patient with a gastroileal anastomosis reported by Brown and associates and in one reported by Landry.

The losses of fecal fat and nitrogen after gastroileostomy have been quantitated in only a few cases.[4,5,12,21,36,46] Presumably quantitative studies have not been performed more frequently because the presence of undigested food in the stools was evident on gross inspection. Usually the stools have been described as grossly steatorrheal, and in numerous instances microscopic examination has confirmed the presence of excess fat and undigested muscle fibers. The magnitude of the steatorrhea expressed as per cent of dry weight of the stool was found to be 30.2%,[12] 33%,[5] and 63.6%[36] in three cases so evaluated, and Smith and Walters mentioned encountering values up to 62%. Intake-excretion studies have been reported only twice before; in both cases partial gastrectomy had been performed at the time of gastroileostomy: Fleming and Ward-McQuaid found "81% absorption" in one patient on an unspecified diet, the anastomosis being 40 cm. above the ileocecal valve. Brine and Fraser's patient had an anastomosis of the ileum to the gastric remnant at the same level (18 in. [45.7 cm.] above the ileocecal valve) and was studied while eating a 90 gm. fat diet; a four-day stool collection revealed that the average daily value for fecal fat was 53.6 gm., and the average daily excretion of fecal nitrogen was 9.7 gm. in this case. Our patient (Case 4) was studied while receiving a standard 100 gm. fat diet.[50] Analysis of a two-day collection of stools showed an average daily excretion of fat of 32 gm. and of nitrogen of 4.4 gm. This patient also had a jejunocolic fistula, which well may have been the principal factor in the pathogenesis of these losses.

Dehydration and Other Malabsorptive Effects.—Patients with a gastroileal anastomosis may lose large amounts of water and electrolytes in the stools and emesis. Dehydration is described commonly in such patients. Although, as noted above, hypokalemia and marked depletion of body stores of potassium have been reported only infrequently after gastroileostomy, hypocalcemia has been mentioned more commonly,[2,4,12,14,35,38,48] and in the remarkable case of Cooley and Hartmann chemical osteomalacia and multiple pseudofractures had occurred six years after the gastroileostomy; the patient had even become addicted to opiates employed to relieve the skeletal pains. Glossitis and peripheral neuritis, as in Case 1, have been described occasionally, as well as prolongation of the blood prothrombin time and lowered levels of serum carotene and plasma ascorbic acid (vitamin C). Hypoproteinemia and peripheral edema have not been uncommon. Kogan and associates stated that a flat glucose-tolerance curve is of diagnostic help in cases in which gastroileostomy and subtotal gastrectomy have been combined.

Roentgenologic Findings.—Roentgenologic study of the stomach or colon may confirm the presence of a gastroileal anastomosis or sometimes establish its presence when the lesion was previously unsuspected. Roentgenologic studies, however, have not been diagnostic in a fair proportion of the cases.[43,46] In this regard Brown and coworkers have emphasized the diagnostic value of observing refilling of the stomach by barium after it has emptied and have stressed the importance of making serial gastrointestinal roentgenograms. Others[43,46] also have found this technique worth-while. The presence of a gastroileal anastomosis was established roentgenologically in only two of our five cases. Not uncommonly a gastroileal anastomosis is misinterpreted roentgenologically as a gastrojejunocolic fistula, and such misinterpretation may tend to be misleading, as in our Case 1. The physician, therefore, should place more de-

pendence on the clinical picture than on the roentgenologist's inability to demonstrate a gastroileal anastomosis.

Differential Diagnosis

Gastrojejunocolic fistula is the lesion most likely to offer confusion in the differential diagnosis of gastroileal anastomosis. In this connection it is helpful to keep in mind that gastrojejunocolic fistula is rare in women, it almost always follows posterior gastroenterostomy done without gastrectomy, and, as Lowdon and others [46] emphasize, it almost never produces symptoms within a month of operation. Symptoms of gastrojejunocolic fistula usually begin at least four months after operation and usually are preceded by abdominal pain characteristic of gastrojejunal ulceration. As Lahey and Sedgwick have observed, gastrojejunocolic fistula is much less frequent after gastrojejunostomy combined with subtotal gastric resection than after gastrojejunostomy alone.

Nontropical sprue and external pancreatic insufficiency secondary to chronic relapsing pancreatitis or to carcinoma or calculus occluding the main pancreatic duct, regional enteritis, and chronic ulcerative colitis are other conditions which must be distinguished from a gastroileal stoma. Lacking other telltale clues, such as fecal belching or vomitus, proctoscopic visualization of ulcers, roentgenologic demonstration of a gastroileal anastomosis, skip lesions and skip areas in the small bowel, or pancreatic calcifications, these other conditions become less likely possibilities when there exists the suspicious circumstance that the steatorrheal diarrhea and progressive loss of weight began within a few days of an operation for ulcer. Postgastrectomy steatorrhea is usually mild, but when vagotomy has also been performed, the clinical picture may simulate that due to gastroileostomy. Roentgenologic examination of the stomach and small bowel may assist in the differentiation of these conditions.

In four cases [4,18,20,36] a gastroileal anastomosis has been encountered in association with anomalous (incomplete) rotation of the intestines, the colon lying entirely in the left side of the abdomen. Such anomalous rotation may add to the difficulties in differentiating the proximal portion of the jejunum from the ileum at operation. The occasional inadvertent gastroileostomy points up the fact that in every case in which gastrojejunostomy is performed the surgeon should note carefully the anatomic arrangement prior to the making of the anastomosis and again before closing the abdomen. By so doing it should be possible to detect the presence of any anomalous arrangement and avoid the embarrassment of a gastroileal anastomosis.

Summary

Gastroileostomy should be strongly suspected in any patient in whom lienteric or steatorrheal diarrhea begins within a week or two of an abdominal operation because of peptic ulcer. Progressive loss of weight with unimpaired appetite, abdominal pain which may be of ulcer type, fecal belching, fecal vomiting, malnutrition, dehydration, and variable evidences of depletion of body stores of vitamins and electrolytes through loss in the stools complete the clinical picture.

In some cases the typical syndrome does not develop after gastroileostomy. Five cases are described to illustrate some of the vagaries in the clinical features referable to gastroileal anastomosis. In one patient hypokalemia and marked potassium deficit dominated the clinical picture and required intensive intravenous and oral treatment with potassium for eight days before the corrective operation.

Gastrointestinal roentgenologic studies, although often helpful in demonstrating the presence of a gastroileal anastomosis, are not infrequently misleading in that they may fail to do so when a gastroileal stoma actually exists.

Mayo Clinic.

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A Follow-Up Study of Hereditary Chronic Nephritis

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In 1951 we reported the genetically predictable occurrence of chronic renal disease with associated nerve deafness in a large family.[1,2] One hundred thirty-four members of the family were examined, and adequate clinical data were available concerning three of seven males in the family who had died of uremia in the recent or remote past. Of the 44 members involved, 43 had pyuria, 32 had hematuria, all had cylinduria, and for 17 of 32 studied, the urine cultures were positive for bacteria. Of 59 patients studied, 14 had abnormal audiograms. Five of those with hearing deficits showed no evidence of renal disease at the time of examination, but two of these were found to be carriers of the trait for renal disease in that the renal lesion was observed in their descendants. Microscopic sections from one postmortem examination showed severe, diffuse interstitial pyelonephritis with inflammatory infiltrate, microscopic abscesses, normal glomeruli, and atrophic and dilated tubules. The pattern of inheritance was compatible with that of a partially sex-linked dominant trait. The disorder segregated in distinct family lines, and the disease did not appear subsequently in uninvolved branches of the family.

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Although other instances of so-called "familial nephritis" had been reported prior to 1951,[3-5] in only one of these was there associated nerve deafness. In this family [4,5] several patients had hematuria, positive urine cultures, and deafness. Sine 1951, however, several reports of hereditary renal disease with associated nerve deafness have appeared in the literature,[6-12] and the existence of at least two additional families is known.[13,14] Goldbloom et al.[6] described four members of a single family group with renal functional impairment; two had bilateral nerve deafness; in addition, one had an abnormality of the ocular lens. Two of their patients showed severe chronic pyelonephritis at autopsy. An additional and most interesting pathologic feature was the presence of grossly visible fatty streaks in the kidneys of one patient and microscopically apparent fat-filled macrophages in the kidneys of both these patients. Sohar [7,8] studied four Israeli brothers who presented hyposthenuria, minimal urinary sediment changes, proteinuria, nerve deafness, and ocular abnormalities. Urine cultures were sterile, and histologic data were not available. Poli [9] examined a large family in Italy in which many members had hematuria and proteinuria, and several had deafness of unknown type. At autopsy the kidneys were seen to be small and contracted, and the published photomicrographs showed intense interstitial inflammation, dilated tubules, and periglomerular fibrosis. Hamburger et al.[10] also described a large family with renal disease and associated nerve deafness, but the details of their studies are not available to us for critical review. Reyersbach and Butler [11] and Sturtz and Burke [12] each described the hereditary occurrence of

a disease characterized by hematuria and nerve deafness in which renal biopsy in one case [11] showed normal glomeruli with red blood cells in the tubules. In one of these families [12] the renal disease apparently was progressive. Robin et al.[13] described a family in which renal disease and nerve deafness appeared to be on an inherited basis. The mechanism of inheritance was thought to be a partially sex-linked dominant. Histologically these patients showed interstitial pyelonephritis. In addition, these authors carried out extensive studies of the family originally described by Reyersbach and Butler, whose patients had clinical manifestations and a pattern of inheritance similar to those seen in Robin's family with pyelonephritis. Several autopsies performed on members of Reyersbach and Butler's family showed chronic glomerulonephritis. One other family [14] is known to exist in which the findings are similar to those presented here.

The rapid appearance of so many reports of hereditary renal disease with features similar to those observed in our patients suggests that these various and widespread families may all suffer from the same or related diseases. This, plus the desire to confirm and extend our original observations with newer techniques of study now available to us, prompted a resurvey of this large group.

Material and Methods

One hundred sixty-eight members of the original family reported in 1951 were examined in the present study. Of these, 97 had been seen previously; 71 were new subjects. On each, a brief history was taken and physical examination and urinalysis were performed. Urinalyses were considered abnormal if the urine showed one or more of the following changes: (1) 5 to 10 or more leukocytes per high-power field in the centrifuged sediment; (2) 5 to 10 or more erythrocytes per high-power field; (3) proteinuria; (4) many casts; (5) clumps of leukocytes; (6) leukocyte casts, or (7) erythrocyte casts. In addition, if leukocytes, erythrocytes, and casts were all present, the urine was considered abnormal, even though the numbers of each kind of cell per high-power field were less than 5 to 10. In almost every urine considered abnormal, more than one of these criteria was satisfied.

In 12 cases, urine cultures were made on blood agar and eosin-methylene blue agar and in thioglycolate broth. Percutaneous renal biopsy was carried out in five patients, and one complete autopsy has been performed. Audiograms were made in 86 patients.

As a means of studying the possible role of anomalous abdominal lymphatics in the pathogenesis of the renal disease in these patients, I^{131}-labeled glycerol trioleate * was administered to one patient from this family, two patients with sporadic chronic pyelonephritis, one patient with severe chyluria, and two normal subjects. One hundred microcuries of I^{131}-labeled glycerol trioleate prepared according to the technique of Sanders et al.,[15] was administered orally one hour after the patient had ingested 1 liter of water. Blood samples were drawn at 15-minute intervals for one hour and hourly thereafter for three hours. The radioactivity was determined directly on heparinized whole blood in a well-type scintillation counter. Urine samples were collected at 15-minute intervals for two hours and hourly thereafter for two hours. Urine 40 ml. and chloroform 4 ml. were shaken for 30 minutes in a Kahn shaker, and the emulsions were broken by the addition of small amounts of isopropyl alcohol and sodium chloride, followed by centrifugation. The radioactivity in the chloroform extracts was determined in the scintillation counter. Recoveries of added I^{131}-labeled trioleate averaged 85% to 90% with this technique.

Urines from 13 normal subjects and from 8 involved and 12 uninvolved members of the family were chromatographed for amino acids. All chromatograms were made with Whatman No. 1 filter paper, tertiary butanol, methyl ethyl ketone, water, and diethylamine (40, 40, 20, 4) being used for the first dimension, and *n*-butyl alcohol, glacial acetic acid, and water (200, 30, 75) for the second dimension. Ninhydrin was used for staining.

The 71 new subjects examined during this survey, when added to those examined initially and to those for whom adequate clinical data are now available from other physicians, make a total of 217 members in this single family for whom data are available for analysis.

Clinical and Laboratory Findings

Of the 168 persons examined during the present study, 64 were male and 104 were female. Of 71 new subjects, 28 were males and 43 females. Of 97 reexaminations, 36

* Obtained from Abbott Laboratories, Oak Ridge, Tenn.

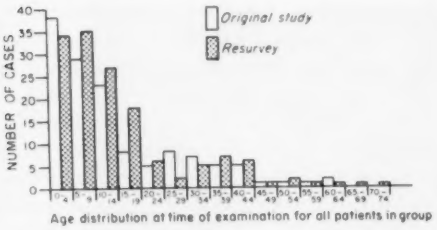


Fig. 1.—Age distribution at the time of examination for all patients in the group.

were in males and 61 in females. The age distribution of patients examined in comparison with that at the original examinations is shown in Figure 1. Although the two groups are quite similar, the ages of the majority of the subjects available for study reflect the five-year interval elapsed since the original study. The large peak at 0 to 4 years represents new members of the family born since the original study. Although a few subjects gave a history of intermittent costovertebral angle tenderness, nocturia, or dysuria, most of them were asymptomatic, and gross pyuria, fever, and malaise were unusual features. Three additional males and one female had died in uremia since the original study.

Of the 49 definitely abnormal urines, 8 were from males and 41 from females. Two males and twenty-one females were new cases; the others were known to be abnormal from the earlier studies.

The incidence of the definitely abnormal urinary findings in the survey, in comparison with that found in the original examinations, is shown in Figure 2. Pyuria was present in 49, hematuria in 39, cylindruria in 39, and proteinuria in 20 patients. One person had red blood cell casts; nine had clumps of white blood cells in the urine. With the exception of proteinuria, all urinary abnormalities occurred in the same relative incidence as in the original study. It is of interest that the number of patients with proteinuria had increased from 8 among 44 examined in 1949 to 20 out of 49 examined in 1956. One of these was a 16-year-old girl who had had pyuria, hematuria, cylindruria, and a urine culture positive for Aerobacter aerogenes in 1949. She was treated with sulfadiazine at that time. The only abnormal finding in her urine at this time was protein. This patient belongs to Generation IV in this family, as do the majority of those available for restudy. It seems likely that the increased incidence of proteinuria found in the resurvey represents the result of progression of a chronic disease in these patients, most of whom now have had the disorder for an additional six years.

Thirty-seven urine cultures were made from 12 patients. Escherichia coli was found in both of two cultures from a woman who died in uremia; microaerophilic alpha hemolytic streptococci were present in two cultures from a 4-year-old girl; microaerophilic beta hemolytic streptococci were found in one of two cultures of a 29-year-old woman, and E. coli was found in one of three cultures from a 26-year-old woman. In the other eight subjects, the urine cultures were repeatedly negative, although Gram-positive cocci were found consistently in stained urine sediments from two of the eight. Intravenous pyelograms were normal in six of the eight subjects in whom this examination was performed. Another showed blunting of the calyces of the left kidney. Intravenous pyelograms were attempted in the female patient with uremia, but the visualization of the kidneys was inadequate. Phenosulfonphthalein and concentration tests were normal in seven of the eight subjects; in the eighth, who was

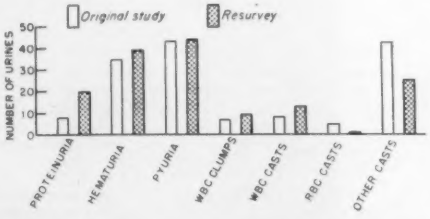


Fig. 2.—Incidence of abnormal urinary findings in this survey as compared with that of the original study.

TABLE 1.—*Relationship of Nerve Deafness to Renal Abnormalities*

Category	Male	Female
Kidney abnormal Hearing abnormal	13	1
Kidney normal Hearing normal	22	44
Kidney abnormal Hearing normal	2	21
Kidney normal Hearing abnormal	6	0
Kidney abnormal Hearing doubtful	1	2
Kidney doubtful Hearing normal	1	4
Kidney doubtful Hearing abnormal	0	0
Kidney doubtful Hearing doubtful	1	0

uremic, both functions were severely reduced.

Eighty-six audiographic studies were performed. The audiograms of 20 males and 1 female showed high-tone deafness. Two males and four females had abnormalities in the high-tone range of doubtful significance. The relationship of the hearing loss to renal involvement is examined in Table 1. It can be seen that 13 males and 1 female showed both abnormalities, whereas 22 males and 44 females had neither. Twenty-three patients, only two of whom were male, had had normal hearing with definite renal disease. Six males had hearing loss with normal urines. At least one of these was a carrier for the renal abnormality. The association of the hearing loss with the clinically evident renal lesion, therefore, while not perfect, seems definite, and is similar to the findings in the earlier studies.

Pathologic Anatomy

A. Kidneys.—The major clinical and pathologic findings in the six patients for whom additional pathologic data are available are shown in Table 2. The patients are listed in the order of their ages, since the pathologic changes increased with age. Percutaneous renal biopsy in the two young girls (Cases 1 and 2) showed only a few

TABLE 2.—*Pathologic Anatomy*

Patient No.	Pedigree No. Age; Sex	Description Specimen	Histologic Findings	Diagnosis of Renal Disease
1	IV-174 13 F SC 17793	Needle biopsy 11×1 mm. Cortex and medulla	Slight thickening of basement membranes of Bowman's capsules; one hyalinized glomerulus; no inflammation; a few red blood cells in tubular lumens	None
2	IV-173 15 F SC 17792	Needle biopsy 6×1 mm. Cortex and medulla	Thickening of basement membranes of Bowman's capsules; two hyaline glomeruli; no inflammation; red blood cells in the tubular lumens	None
3	IV-4 28 F SC 17880	Needle biopsy 10×1 mm. Cortex and medulla (serially sectioned)	Arteriosclerosis; focal glomerular sclerosis and thickening of capsular basement membranes; few hyalinized glomeruli; focal tubular atrophy and interstitial fibrosis; tubular and interstitial lipid deposits; few focal lymphocytic infiltrations	None
4	III-52 28 F SC 18043	Needle biopsy 6×1 mm.Cortex only (serially sectioned)	Focal thickening of basement membranes of Bowman's capsules; few hyaline glomeruli; few small foci of lymphocytic infiltration	None
5	III-19 44 M SC 1665	Autopsy: both kidneys (6×4×2.5 cm.), about 70 gm. each, coarsely granular surfaces with yellow cortical streaks	Diffuse cortical scarring with alternation of atrophy of convoluted tubules; focal tubular hemorrhages; hyaline droplets and lipid in epithelial cells; large foci of interstitial foam cells containing anisotropic lipid; severe arterio- and arteriolosclerosis; glomeruli hypercellular, ischemic with epithelial crescents and capsular hemorrhages	Chronic glomerulonephritis
6	II-17 62 F SC 18525	Postmortem needle samples —3 pieces 10×1, 10×1, and 5×1 mm.; cortex only	Diffuse cortical scarring with atrophic and occasional hypertrophic tubules, some containing hyaline droplets; many hyaline glomeruli; others have thickened capsules; occasional "waxy" masses in glomerular tufts; occasional hyaline arteriole	Unclassified nephrosclerosis

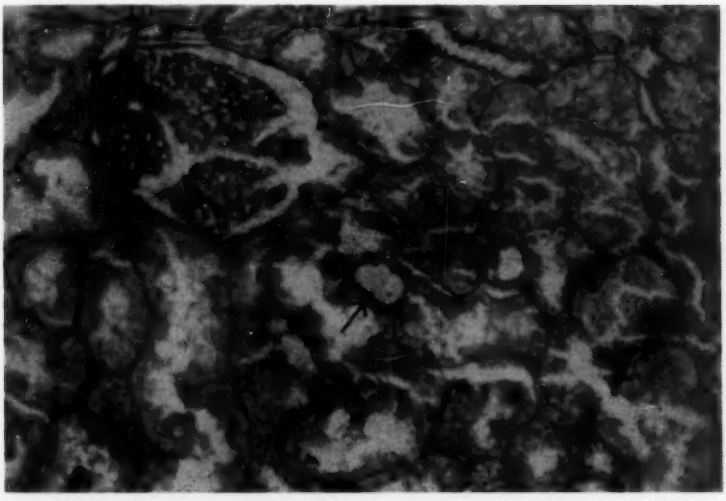
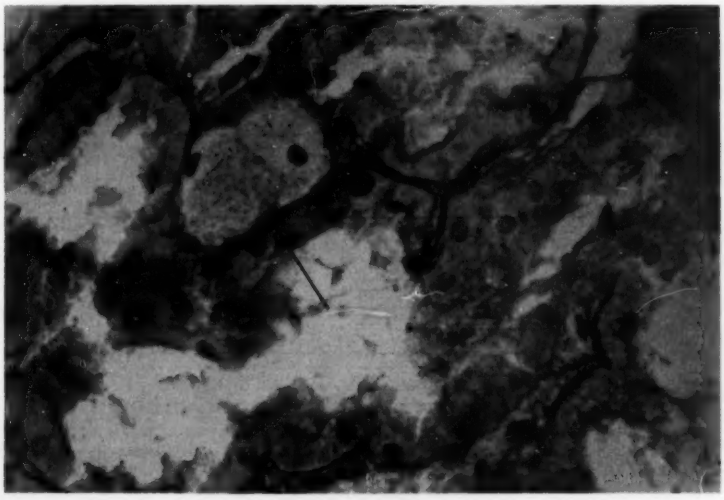


Fig. 3 (Case 3).—Low-power photomicrograph of the renal biopsy specimen; periodic acid-Schiff stain. The glomerulus shows thickening of the fibrous material of the stalk and focal thickening of Bowman's capsule. In addition, two foam cells (arrow) are seen to the right of the glomerulus.

red blood cells in the tubules. Although a few of the glomeruli were hyalinized, the majority were completely normal. Aside from the hyaline glomeruli, the only abnormality the biopsy specimens had in common was a focal thickening of the basement membranes of Bowman's capsule without pericapsular fibrosis. This was impressive chiefly because of its occurrence as an isolated abnormality in the two youthful patients. Two patients (Cases 3 and 4) in the third decade of life showed the same numbers of hyalinized glomeruli as were found in the biopsy specimens from the young subjects. Focal thickening of the basement membrane of Bowman's capsule

Fig. 4.—High-power magnification of the foam cells in Figure 3.



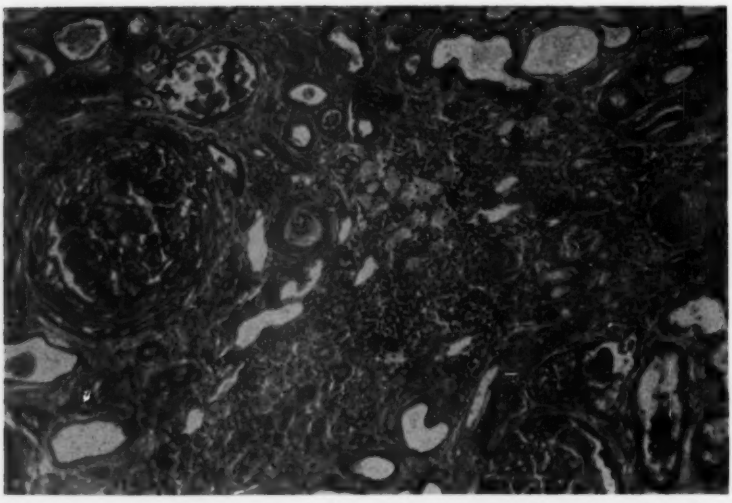


Fig. 5 (Case 5).—Photomicrograph of the kidney; hematoxylin-eosin stain. Numerous foam cells are seen scattered throughout the interstitial tissues. The glomerulus shows a characteristic crescent. Moderate interstitial lymphocytic infiltrate is present.

was also present. In Case 3 there was some thickening of the fibrous material in the stalk or tufts of an occasional glomerulus. In addition, the biopsy in Case 3 revealed a few small foci of large, pale, foamy cells, which resembled fat-filled macrophages, scattered throughout the specimen. In Figures 3 and 4, the foam cells found in the biopsy specimen are shown at low and high magnification, together with the histologic features of the neighboring glomeruli and tubules. Although a fat stain could not be made, the foam cells were presumed to have contained lipid; they were identical in appearance to the cells in Case 5.

Autopsy in Case 5, a man who died at age 43, showed much more advanced changes. The kidneys were small and contracted. The capsules were adherent. The renal cortex was markedly reduced in thickness, and the medullary architecture was disrupted. There were no abnormalities of the pelvis, ureters, or urinary bladder. Microscopic examination suggested a histologic diagnosis of chronic glomerulonephritis. Some of the glomeruli were normal; others lay embedded in layers of thick periglomerular fibrosis, and some were completely hyalinized. Many glomeruli showed the epithelial crescents characteristic of subacute glomerulonephritis, but the small dimensions of the kidneys and the extent of tubular atrophy and cortical scarring indicated greater chronicity. Distinct arteriolosclerosis was also present and was in keeping with chronicity of the disease. The interstitial tissue showed moderate lymphocytic infiltration and severe scarring. A notable feature was the presence of many large interstitial deposits of lipid-laden phagocytes, similar to those described by Goldbloom et al.[6] in two young boys with hereditary pyelonephritis. The cells contained dissolved anisotropic material, as did the tubular epithelial lipid deposits. These findings are shown in Figures 5 to 7.

In the other fatal case (Case 6), the samples examined indicated a similarly diffuse renal disease with marked cortical scarring and atrophy of nephrons. However, the glomeruli differed from those in the foregoing case. They varied in structure from essentially normal to completely hyalinized. Neither epithelial crescents nor endothelial proliferation was present. Some glomeruli contained localized lumpy hyalin

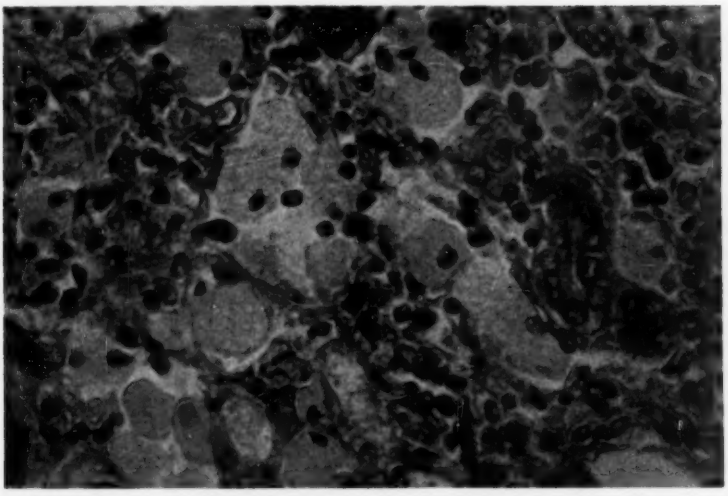


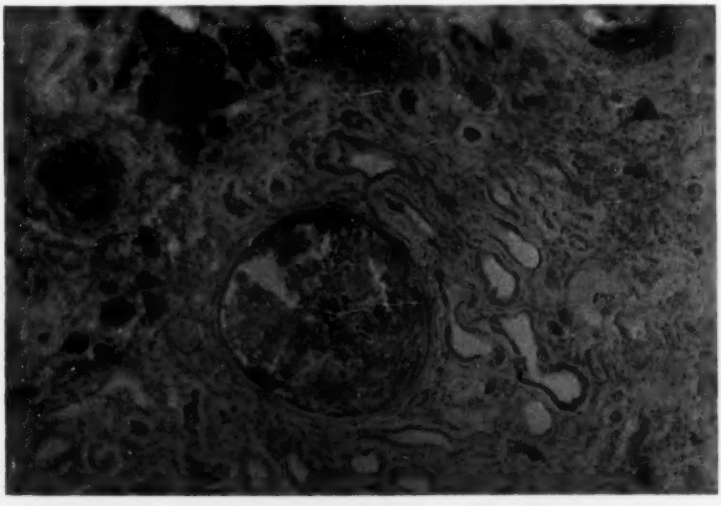
Fig. 6 (Case 5).—High-power magnification of the foam cells.

masses, apparently altered capillary basement membranes. There were intimal thickening of small arteries and arteriolosclerosis, as well as foci of lymphocytic interstitial infiltrate.

Although a few small foci of lymphocytes were found in the sections from the adult patients, there was no tubular exudate. The histologic evidence for renal infection in these cases, therefore, was not as striking as in the sections presented previously. Of interest, however, is the fact that at the time of renal biopsy in Case 4, E. coli was cultured from the biopsy specimen, even though a histologic diagnosis of pyelonephritis could not be made.

B. Inner Ear.—The petrous ridges and lateral portions of the calvaria were re-

Fig. 7 (Case 5).—Fat stain of the kidney. Note the intense staining of the foam cells.



moved at autopsy in Case 5. Dr. Victor Goodhill, Los Angeles, furnished the sections of this material.

There was hyperostosis at the tip of the cochlea and in other sites which could not be localized accurately, but other abnormalities were not noted. Unfortunately, the stapes and oval window could not be identified because of the plane of the sections. In addition, cellular detail was poor, so that adequate evaluation of the organ of Corti was not possible. None of the foam cells which characterized the renal lesion in this patient could be demonstrated in the ear.

Inheritance

Because of the nature of the trait in question, the accuracy and efficiency of the methods of diagnosis of the presence or absence of renal disease must be considered. In all, 211 persons have been examined; 97 of these were seen on at least two occasions after an interval of at least six years. Of these, 84 showed the same urinary findings as in the initial study. Of the 13 patients whose urinary findings were different from those found earlier, 3 had been abnormal and were now normal; 2 of these had had chemotherapy; the other had not. Five were persons who had become abnormal since the earlier study was completed. Three others had been normal earlier; their urines were now questionably abnormal. Findings for one had been doubtful, then abnormal, and for one doubtful, then normal, on the two examinations.

Figure 8 is a pedigree chart showing the involved members found in either the initial study or the resurvey. Several members of Generation III have transmitted the trait to their children, although they showed no urinary abnormalities. It should be noted that most of the members of Generation IV have not yet had children. Thus, any such

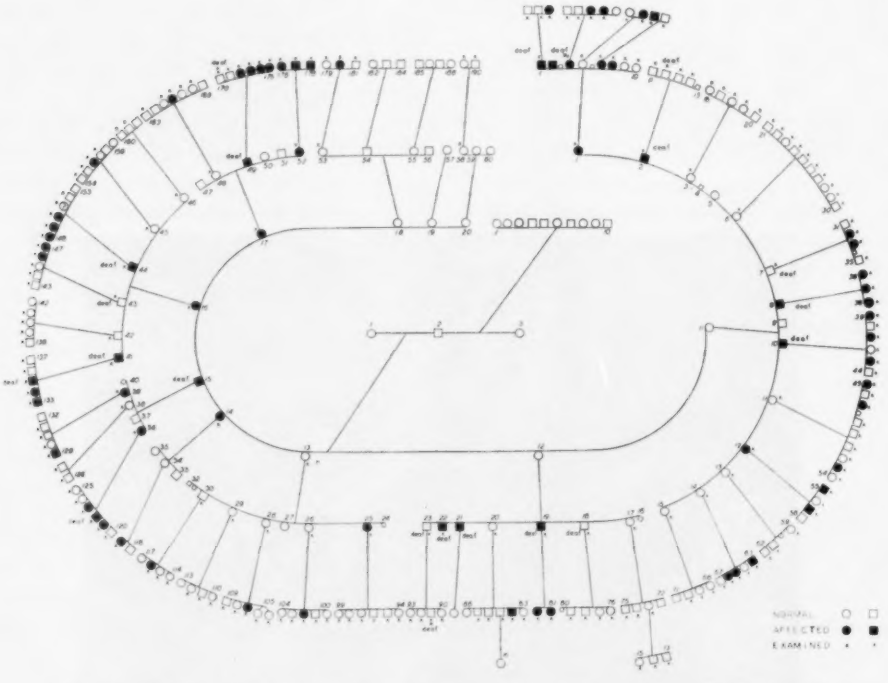


Fig. 8.—Pedigree chart combining the data from the resurvey with those of the original study.

TABLE 3.—*Analysis of Involved Families*

Number of Subjects	Members Involved	Carriers	Total	Expected	Incidence, %
202	74	16	90	101	44.5

carriers present in this generation could not be recognized at this time.

The results of the analysis for dominance, carried out using all the offspring of involved or known carrier members, are shown in Table 3. There were 202 of these children available for analysis. Of these, 90 either showed abnormalities in the urine or were found to be carrier subjects. This is an actual incidence of 44.5%, as compared with an expected incidence of 50% in Mendelian dominant inheritance. However, addition of the carrier subjects who are not yet recognized in Generation IV would decrease this deviation, making it likely that the trait for renal disease is a dominant trait.

Further analysis of the data suggests that the trait is sex-linked. Sex linkage was evaluated by studying the offspring of affected males. If a trait is sex-linked and if the gene has been received by an affected male from his mother, it will be on the X-chromosome and will be transmitted, therefore, to his daughters. If the defective gene has been received from his father, it will be on the Y-chromosome and will be transmitted to his sons. Table 4 shows data for the children of affected males, all of whom received the trait from their mothers and, therefore, carried the trait on their X-chromosomes. The data can be explained on the basis of a sex-linked dominant with the exception of two affected males and five normal females.

That these seven members who are exceptions to the hypothesis of sex-linked dominance represent instances of crossing over (partial sex linkage) is not certain. The five normal females are as follows:

III-38 39-year-old woman—normal on two occasions (has two sons who have been normal on two occasions)
IV-42 13-year-old girl—normal on two occasions
IV-146 16-year-old girl—normal on three occasions
IV-114 5-year-old girl—normal on one occasion
IV-115 4-year-old girl—normal on one occasion

In spite of the fact that three of these patients have been examined on multiple occasions, the presence of carrier females in this family makes it apparent that a female can carry the trait for renal disease and still show no abnormalities on urinalysis. It cannot be stated with assurance, therefore, that the five females in question do not carry the trait.

That the two involved males represent instances of crossing over seems more likely.

TABLE 4.—*Analysis of Offspring of Affected Males Who Derived the Trait from Their Mothers*

Kindred No. of Parent	Males			Females		
	Affected	Normal	Condition Unknown	Affected	Normal	Condition Unknown
II-15	0	1		2	1	1 (sex unknown)
III-2	0	4	1 (stillborn)			
III-7	0	2	1 (died in infancy)	2	0	
III-8	0	0		3	0	
III-10	0	2		3	1	
III-19	0	0		2	0	
III-30	0	0		1	2	1 (infant)
III-41	2	2		1	0	
III-43	0	2		2	1	
III-44	0	1	1 (infant)	3	0	1 (questionable on test)
III-49	0	2		4	0	
IV-1	0	2		1	0	
	2	18	3	24	5	3

These subjects are the same two reported previously, but their ages as given in the initial report were incorrect.[1] One (IV-133) is now 20 years of age and was found to have an abnormal urine during both studies. The other (IV-135) is 12 years old and has been found to be abnormal on three separate occasions. In addition, it is of special interest that the audiogram on IV-135 shows his hearing to be abnormal. The audiogram of IV-133 also shows some high-tone loss, but this is not sufficient at this time to permit classifying his hearing as definitely abnormal.

Deafness

Audiograms were obtained on 86 members of the kindred. Five male members who had died of pyelonephritis before the study began were known to have been deaf. One who died was not known to have been deaf but was never examined. Only one female (IV-4) developed the characteristic nerve deafness. In all, 20 males and one female were classified as having defective hearing. One female (II-12) married a man who had otosclerosis. Deafness in her descendants was not considered a manifestation of the characteristic nerve deafness.

Although nerve deafness usually manifested itself in males as the renal disease became severer, in several instances it appeared in a male member who did not have renal disease. Although this suggests the possibility that the deafness is due to a separate gene, possibly a sex-linked recessive, four males (III-2, III-41, III-49, and III-23) have transmitted the deafness to a son, contradicting the hypothesis of a separate sex-linked recessive inheritance of the deafness. Rather, the data favor the suggestion that the nephritis and the deafness are related in some unknown way. The finding of deafness in other families with a similar renal lesion supports this postulate.[5-14]

Miscellaneous Studies

It has been suggested that anomalous gastrointestinal-renal lymphatics could be responsible for the bilateral character of sporadic pyelonephritis and the enteric etiology of the infection.[15] To evaluate this presumed source of infection, one patient, two normal subjects, and two patients with sporadic pyelonephritis, were given I^{131}-labeled trioleate. In Figure 9 the results in the cases were compared with those obtained when this material was administered to a 62-year-old woman with classical chyluria in whom renal infection could not be demonstrated. The chloroform-soluble radioactive substance appeared in the urine in all instances in a pattern independent of absorption into the blood stream. The chloroform-soluble radioactivity in the urine of the involved member of this pedigree, of the patients with sporadic pyelonephritis, and of the normals reached a total of approximately 1000 cpm/10^8 cpm administered, whereas in the patient with chyluria 400,000 to 800,000 cpm/10^8 cpm administered was recovered. Thus, although a minute amount of gastrointestinal-renal lymphatic back-flow may be present in normals and in patients with renal disease, the degree to

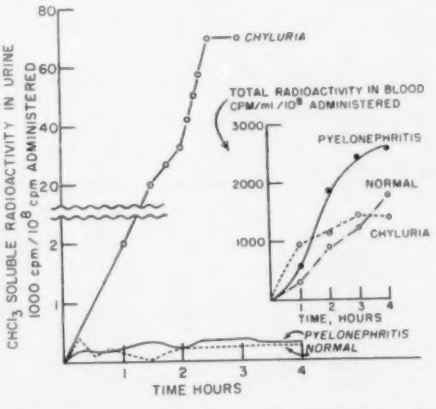


Fig. 9.—Urine and blood radioactivity after the administration of I^{131}-labeled trioleate. Because they were the same, the data from the patient with hereditary chronic nephritis are included with those from the patients with sporadic pyelonephritis.

which this is present does not approach that in the patient with chyluria. This source of the renal infection, therefore, while not excluded by these studies, seems unlikely.

Because of the possibility that some alteration in the mechanisms for resisting infection was responsible for the renal disease in our cases, heat-labile complement-dependent antibacterial activity of the serum was determined in two of our cases as an indirect measure of the properdin system.[17] In these two cases, low-normal values were obtained, but the significance of these data is uncertain. Further studies of the mechanisms for resistance to infection in these patients would be of interest.

In addition, urine from 8 involved and 12 uninvolved members in this family was chromatographed for amino acids in a simple two-dimensional system. No qualitative abnormalities were found. Although exact quantitation of the urinary amino acids has not been carried out, all of the amino acids were present in the same amounts as in simultaneously examined normal control urines.

Comment

Nature of the Disease.—The clinical findings of pyuria, hematuria, proteinuria, and cylindruria in our original studies of this family remain the major abnormalities, both in new cases and in those restudied after six years. While the severity of the disease apparently is greater in male members, three more having died in uremia, one woman in the kindred has now died of uremia, and the most severely involved living patient is female. The associated deafness is present in the same proportion as before. In contrast to some of the other reported families,[6,8-10] none of these patients has ocular lesions.

The clinical evidence for the presence of renal infection in our patients at some time during the course of their disease is strong. The repeated demonstration of pyuria, the cultures of urine which have frequently been positive for organisms known to produce pyelonephritis, and the repeatedly favorable response to appropriate chemotherapy for individual episodes of genitourinary infection,[1] all support this view. In addition, signs of renal infection have been present at autopsy in some of our patients and in patients from other families in which a similar disease is inherited.[6,9,14] Although the children in two of the other reported families manifest hematuria as their major symptom,[11,12] our patients also show a high incidence of hematuria, particularly in young persons.

In spite of these facts, however, except for the autopsy presented originally,[1] the specimens now available for study reveal changes which are different from those of classical pyelonephritis. The presence of foam cells in the biopsy specimen from one young woman, the large numbers of these cells found in the kidney at autopsy in one of the late cases, the epithelial crescents present in the same section together with periglomerular fibrosis and lymphocytic infiltration, and the scattered lymphocytic infiltrates in the other specimens, all suggest that features of both pyelonephritis and glomerulonephritis may be present in varying degree in these patients. In this regard, it may be noted that the same kinds of pathologic changes have been found at autopsy [18] in one patient from the family originally reported by Reyersbach and Butler.[11] The findings in the kidneys of their patient were identical with those in our Case 5, with masses of foam cells and interstitial lymphocytic infiltration without abscess formation. Characteristic glomerular crescents were also found. The diagnoses made were chronic glomerulonephritis and interstitial nephritis. Nerve deafness was also present.

The observation of the same anatomical findings in our Cases 3 and 5 and the cases of two other families [6,11] strongly suggests that all of these patients have the same disease. Since neither the total clinical picture nor the anatomical findings are characteristic of either typical glomerulone-

phritis or typical pyelonephritis, until such time as the basic genetic mechanism for the disease has been identified, it would seem appropriate to designate these cases as instances of hereditary chronic nephritis of unspecified type with a high incidence of superimposed renal infection.

The exact nature of the basic mechanism remains unclear, but more information can now be brought to bear on this problem. Evidence for the presence of abnormal gastrointestinal-renal lymphatic connections has not been found. Likewise, gross anatomical anomalies of the genitourinary tracts were not demonstrable in our patients by pyelography or at autopsy, and no such abnormalities have been found by others. In addition, early in the course of the disease renal tubular function is normal in these patients insofar as phenolsulfonphthalein excretion, concentration tests, and amino acid chromatography are measures of tubular function. Serum antibacterial activity is likewise not definitely abnormal in these persons.

Examination of the histologic specimens, however, has revealed two new findings of possible importance. First, the pathologic changes found in the kidneys become progressively severer as the age of the patients examined increases. Whereas marked changes in the kidneys are found at autopsy, renal biopsies performed in affected children who have marked abnormalities of the urinary sediment show only minimal changes. Second, the finding of a few foam cells in the biopsy tissue of the 29-year-old affected woman, and the demonstration of many of these cells at autopsy in the 49-year-old man give a possible clue to the mechanism that makes the kidneys of these patients susceptible to infection.

Foam cells are not a characteristic histologic feature in sporadic pyelonephritis or vascular nephritis. They are found, occasionally, in small numbers in some patients with the nephrotic syndrome of glomerulonephritis. None of our patients, however, has ever shown the clinical or chemical findings of the nephrotic syndrome. Cells similar to those seen in our cases have been observed in the urine, bone marrow, lymph nodes, spleen, and adrenals of another hereditary disease in which renal disease of unknown nature occurs.[19] In this disorder, angiokeratoma corporis diffusum universale (Fabry), in addition to the tiny cutaneous aneurysms, hyposthenuria, proteinuria, and occasional abnormalities of the urinary sediment, also occur.

The presence of foam cells in the kidneys of our patients and in those of others[6,11] suggests one of two major possibilities. First, an anomaly of fat metabolism may exist in these patients, leading in some way to accumulation of fat-filled macrophages in the kidneys. Second, the accumulation of foam cells may represent a local tissue response to some specific metabolic abnormality. Although the mechanism is not apparent by which such abnormalities could lead to infection in these kidneys with such regularity, a relationship between abnormal cells in the kidney and increased susceptibility to infection seems a reasonable possibility. This view could explain the fact that young patients with this disease do not show characteristic pathologic features, whereas the older patients give variable evidences of moderate to severe chronic nephritis, as well as clinical evidence of renal infection.

The relationship between these hereditary nephritides and sporadic pyelonephritis or glomerulonephritis remains a matter for conjecture only. Careful family histories in many patients with sporadic renal disease often yield the history of a high incidence of renal disease in the family. We have observed two families, in addition to the one we have reported, in which there is a high incidence of clinical pyelonephritis, without nerve deafness. It seems likely that some cases of sporadic interstitial pyelonephritis may actually represent instances of inheritance of an anomaly that leads to renal infection, as in our cases. Other patients may have some other local renal metabolic abnormality that makes their kid-

neys particularly susceptible to infection. Further observations in these areas should provide a new avenue for study of the pathogenesis of this common ailment.

Mechanism of Inheritance.—In the previous study of this family, it was pointed out that except for six members, four females and two males, the data fulfilled the requirements of a sex-linked dominant trait. Partial sex linkage was suggested as a possible explanation for these exceptions. Since that time, others have cast doubt on the whole hypothesis of partial sex linkage in man. Morton,[20] in dealing with our initial report, suggested that sex-linked dominant inheritance best explained our data. He felt that the exceptional females were asymptomatic carriers and that the two males had a different renal disease, unrelated to that found in the rest of the family. He concluded that follow-up study would be necessary to establish partial sex linkage. In the resurvey, five females and two males were found to be exceptions to the sex-linked dominant hypothesis of inheritance. The two males, in particular, appear to represent instances of crossing over.

While the data derived from this study alone may not be sufficient to establish the concept of partial sex linkage, the evidence does suggest this mechanism of inheritance in this family. Until a more satisfactory way of accounting for the seven exceptional members is discovered, the evidence for partial sex linkage cannot be completely disregarded. It is hoped that future study of this kindred, with special attention to these subjects, will clarify this problem. Actually, the answer may not be forthcoming until it becomes possible to examine the children of the two exceptional male members.

Summary

A detailed follow-up study of a large family with hereditary nephritis and associated nerve deafness is reported after a six-year interval.

Clinical, laboratory, and genetic data in this study were similar to those originally found. Clinically, the disorder is a chronic nephritis with frequent episodes of bacterial renal infection. The mechanism of inheritance is that of a sex-linked dominant trait, and the findings suggest that crossing over occurs between the X- and Y-chromosomes.

Renal biopsies have demonstrated minimal structural changes early in life and changes with progress with age.

Foam cells were found in sections from the kidneys of some of these patients.

The similarity of the disorder in our patients to that in other families now reported is discussed. Reasons are presented for believing that most of these cases represent the effect of the same abnormal gene.

It is suggested that renal infection in these patients, and perhaps in some of those with apparently sporadic pyelonephritis, is related to a local renal metabolic abnormality of as yet unidentified nature.

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Acute Nonsuppurative Thyroiditis

A Report of Twelve Cases and a Review of the Literature

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During the last five years there has been an increased interest in acute nonsuppurative thyroiditis and, concomitantly, an increased number of accurately diagnosed cases. Whether this can be accounted for by more astute observation and the availability of better diagnostic methods or whether this represents an actual increase in the occurrence of this disease is difficult to evaluate.

Owing to the possibility of an infectious etiology of acute nonsuppurative thyroiditis, the occurrence of four cases in patients living within the area serviced by a 700-bed hospital within a period of 45 days lead me to review the documented cases of this disease seen in the hospital during the last five years. The findings of this study and a review of the literature form the basis of this article.

Material and Results

From June, 1952, to June, 1957, twelve adequately documented cases of acute nonsuppurative thyroiditis were treated as inpatients at St. Luke's Hospital. It is difficult to estimate how many other cases have been seen in the outpatient department or private doctors' offices, because the cases in these categories are not classified as to disease in the hospital record room. Two cases diagnosed as acute nonsuppurative thyroiditis were not included because of lack of confirmatory evidence that this diagnosis was correct. These 12 cases represent an incidence of 0.01% of all hospital admissions, or approximately 3% of those admitted with the primary diagnosis of thyroid disease during this five-year period.

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From the Department of Medicine and the Thyroid Clinic of St. Luke's Hospital.

Nine patients were female, and three, male. Their ages were from 22 to 58 years, with an average of 40.8 years. Most were in their late fourth or early fifth decade. The duration of symptoms prior to admission varied from 1 to 4 weeks, and the total course of the disease was from 3 to 24 weeks in duration, with the majority lasting approximately 1 month.

The commonest presenting symptom was that of pain in the neck or throat. Radiation of this pain to the ear or jaw was noted by three-fourths of the patients, while one case presented as anterior neck pruritis and excoriation thought to be secondary to topical ointment application, although she denied the use of any medication. Another sought medical advice because of sudden inability to button his shirt. Three-fourths noted either diffuse or unilateral swelling in the anterior neck, with these signs and symptoms first appearing from one day to three weeks before a doctor was consulted. A preceding upper respiratory tract infection was recalled by 4 of the 12 patients. Associated symptoms included manifestations of hypermetabolism, particularly irritability, nervousness, sleeplessness, and weight loss. Dysphagia was noted by 11, and fever and chills, usually occurring in the evening, were noted by two-thirds.

The thyroid was enlarged two to three times over the normal size and was extremely tender to palpation in all patients. The gland was uniformly described as "firm" or "hard," with eight patients having overlying erythema, while in four both erythema and warmth were noted.

Radioactive-iodine (RAI) uptake was below 9% in 11 of the 12 patients, the range being from 0.9% to 8.7%. One had the typical clinical findings, course, and biopsy findings showing "subacute thyroiditis," but the RAI uptake was 67.8%. Following a triiodothyronine test, as described by Werner and Spooner,[60] her RAI was 43.8%. Other than this unusually high RAI uptake value there was no doubt as to her diagnosis, and therefore it must be assumed that she had sufficient uninvolved or undamaged thyroid tissue to account for this result. No substernal extension of the thyroid gland was noted by x-ray. The BMR revealed the hypermetabolic state of the early phase of this disease with values of +02 to +32, with most values being in the +20 to +30 range. The erythrocyte sedimentation rate was uniformly high, from 34 mm. to 60 mm. per hour, corrected Wintrobe, while the white blood cell count was slightly elevated in three patients, with normal values and normal differential counts in all other cases.

One patient treated with salicylates and antibiotics had a complete and uneventful recovery without remission or sequelae and was euthyroid upon follow-up studies four years later. Two received antibiotics for one to two weeks and when symptoms did not clear were given radiotherapy with subsequent clearing of all signs and symptoms within one week after treatment was instituted. Both had BMR's of −5 and −7 during the next six months while their sedimentation rates were returning to normal. The two patients receiving steroids and antibiotics had a clearing of all symptoms in one to five days, but one, when steroid therapy was prematurely reduced, had a two-day recurrence of neck pain. Neither showed any abnormality in subsequent tests of thyroid function over a period of 6 to 12 months.

Three patients receiving steroids alone had almost immediate cessation of symptomology without rebound. They were treated with large doses of cortisone or prednisone for three to four weeks, with the dose being reduced gradually over the ensuing two weeks. One patient received a 10-day course of Corticotropin (ACTH) in an attempt to prevent any manifestations of hypoadrenalism. None of these patients exhibited any clinical or laboratory evidence of hypometabolism during their follow-up period. Four patients initially received steroid therapy, but owing to persistence of signs and symptoms of active thyroiditis, radiotherapy was added to their therapy, with remission of all complaints. Two of these patients underwent thyroid biopsy, as suggested by Crile and Hazard,[12] with the diagnosis of "chronic nonspecific thyroiditis." All four patients exhibited clinical symptoms of hypometabolism as expressed by lethargy, weight gain, "lack of ambition," and increased sleep requirements following irradiation. One with a BMR of −15 required ½ grain (32.5 mg.) of thyroid extract per day for two months to control symptoms but has subsequently become euthyroid.

In addition to the above therapeutic agents, all patients were given such nonspecific therapy as analgesics and/or local therapy for pain and discomfort. In 11 of the 12 pain was controlled with ice packs and salicylates, while one required codeine and meperidene for relief.

Three patients on steroid therapy alone were relieved by the first course of treatment, and one patient who had a rebound on steroids and antibiotics exhibited a complete remission after steroid dosage was increased. It was necessary to add a second means of therapy to secure or maintain a remission and prevent a rebound in eight of the patients. In one, cortisone, and in another, the change to a second antibiotic, seemed effective where previous antibiotic therapy had failed. Six patients were given radiation therapy, which was the apparent agent responsible for final and complete relief of all complaints. Two had previously been treated by antibiotics, while four had received steroids. Thus a rebound or lack of initial response occured in 75% of these

Case (Sex)	Date of Onset & Course	Presenting Symptom	Associated Symptoms	Physical Findings	Laboratory Data			
					RAI, %	BMR	ESR, Mm.	WBC
1 (F)	6/8/55-7/5/55 (1 mo.)	Anterior neck pain with radiation to teeth for 3 wk.	Dysphagia	P 100, BP 110/70, temp. 102.2 F; thyroid 2 × enlarged, firm, & tender	3	+24	38-40	8,900 (P-61)
2 (M)	3/25/55-4/28/55 (1 mo.)	Dull ache in anterior neck for 1 mo.	Unable to button shirt, chills & fever, temp. 103 F, night sweats	P 88, BP 150/90, temp. 100 F; Thyroid 1 × enlarged, firm, & tender	7	+21	34	11,700 (P-74)
3 (M)	10/1/55-10/25/55	Tenderness in anterior neck for 3 wk.; URI 1 wk. before	Shirt collar tight, temp. 100 F each day	P 80, BP 126/78, temp. 99.4; thyroid 2 × enlarged, tender, firm	1	+25	36	9,100 (P-70)
4 (F)	9/10/55-1/25/56 (4 mo.)	Pain in anterior neck with Rt. ear radiation for 3 wk.; URI 1 wk. prior to pain	Dysphagia, nightly chills, & fever	P 105, BP 140/85, temp 101 F; thyroid 3 × enlarged, tender, firm; Rt. nodule 2×3 cm.; slightly warm erythematous anterior neck	1	+ 0 —	50	11,550 (P-76)
5 (M)	4/1/55-5/20/55 (2 mo.)	Pain in Rt. anterior neck radiating to Rt. ear for 6 wk.	Slight dysphagia, fever, & chills, with night sweats; temp. 103 F; fatigue & malaise	P 64, BP 120/65, temp 101 F; thyroid 1 × enlarged, tender	5	+19	36	8,450 (P-68)
6 (F)	6/22/50-7/17/50 (1 mo.)	Painful swelling L. anterior neck with L. ear radiation for 1 wk.	Dysphagia, fever; diabetic, urine 3+ to 4+ after previous good control on PZI, 40 units	P 100, BP 120/75, temp. 101 F; thyroid 1 × enlarged, firm, warm, & tender; anterior neck slightly erythematous	None	+27	60	9,400 (P-71)
7 (F)	8/18/56-11/15/56 (3 mo.)	Pain in L. anterior neck for 2 wk.; radiation to L. ear for 1 wk.	Dysphagia & choking sensation; fever; 9 lb. weight loss	P 92, BP 120/90, temp. 101 F; thyroid 2 × enlarged L. lobe, 1 × enlarged Rt. lobe, tender, warm, & firm	2	+20	40	7,500 (P-79)
8 (F)	8/14/56-11/30/56 (3 mo.)	Progressive painful swelling of L. and Rt. anterior neck over 2-wk. period	Dysphagia	P 100, BP 135/75, temp 101 F; thyroid 2 × enlarged, tender, firm, slightly warm, & erythematous	8.7	+13	38	8,800 (P-74)
9 (F)	10/15/56-1/15/57 (3 mo.)	Painful swelling of Rt. anterior neck with radiation to Rt. ear for 4 wk. following URI	10 lb. weight loss over 4-wk. period	P 100, BP 100/60, temp 100 F; thyroid 2 × enlarged, firm, warm, & tender	1.8	+32	36	6,400 (P-73)
10 (F)	8/1/56-8/30/56 (1 mo.)	Painful pruritic swelling of anterior neck for 1 wk.	6 lb. weight loss in 1 wk.	P 100, BP 110/60, temp. 101 F; thyroid 2 × enlarged, firm, tender, with anterior neck erythema & excoriation	67.8	+17	43	6,400 (P-53)
11 (F)	6/1/56-7/9/56 (5 wk.)	Painful swelling in neck for 1 wk. following URI	Dysphagia, fever	P 80, BP 120/80, temp 101 F; thyroid 2 × enlarged, tender, & firm	3	+24	37	9,300 (P-69)
12 (F)	12/1/53-12/31/53 (1 mo.)	Pain in Rt. side of "throat" for 1 wk.	Dysphagia, fatigue, fever, chills, & night sweats	P 80, BP 130/65, temp. 101.4 F; thyroid 2 × enlarged, tender, & firm	5.5	+24	39	14,250 (P-76)

Summary of Cases from St. Luke's Hospital—Continued

Case (Sex)	Treatment				Results	Follow-up			
	Duration	Type		Dose, Route, Frequency		RAI, % (Date)	BMR (Date)	Symptoms	ESR, Mm/1 Hr. (Date)
1 (F)	6/9	Cortisone		300 mg., p. o., o. d.	Symptoms lost after 2 days; temperature normal, recurrence of pain & temperature 2 ×; complete remission after radiotherapy; gland normal size 2 wk. later	36 (9/22)	—5 (9/22)	No complaints, gland normal	4 (9/22)
	6/10			200 mg., p. o.					
	6/11–6/15			100 mg., p. o.					
	6/16			50 mg., p. o.					
	6/17			100 mg., p. o.					
	6/18			300 mg., p. o.					
	6/19–6/20			200 mg., p. o.					
	6/21–6/25			150 mg., p. o.					
	6/26–7/14			75–50 mg., p. o.					
	6/27–7/1	Radiation	R	300 r					
			L	300 r					
2 (M)	4/9–4/14	Mysteclin (tetracycline & nystatin)		1 gm., p. o., o. d.	No change on antibiotics; 1 day complete clearing on cortisone	None	None	No relapse, gland normal	None
	4/20	Cortisone		300 mg., p. o.					
	4/21			200 mg., p. o.					
	4/22–4/28			100 mg., p. o.					
3 (M)	10/21	Cortisone		300 mg., p. o., o. d.	Complete remission in 1 day	25 (1/17)	None	No relapse, gland normal	6 (1/17)
	10/22			200 mg., p. o.					
	10/23–11/3			100 mg., p. o.					
4 (F)	11/18	Cortisone		150 mg., p. o., o. d.	No relief of symptoms until cortisone dose was increased 1 wk. after therapy begun	15 (3/5)	+6 (3/5)	No relapse, gland remained slightly enlarged for 3 mo.	11 (3/23)
	11/19–11/25			75 mg., p. o., o. d.					
	11/18–11/25	Radiation	R	400 r					
			L	300 r					
	11/25–11/29	Cortisone		150 mg., p. o., o. d.					
	11/30–1/11			75 mg., p. o., o. d.					
	12/21–1/11	Thyroid extract		30 mg., p. o., o. d.					
5 (M)	4/10–4/14	Penicillin		600,000 units I. M., o. d.	Temperature became normal in 2 days; complete remission in 3 wk.	None	None	No relapse, thyroid no longer palpable	None
	4/21–4/29	Tetracycline		1 gm., p. o., o. d.					
	4/30–5/18	Acetylsalicylic acid		10 grains (0.65 gm.) p. o., p. r. n.					
6 (F)	6/26–6/29	Penicillin		600,000 units I. M., o. d.	No change on antibiotics; temp 101 F; insulin requirement increased to PZI 60 units; remission with irradiation	None	—5	No further symptoms; thyroid normal; PZI 35 units	20 (9/1)
	6/30–7/4	Chlortetracycline		1 gm., o. d.					
	7/4–7/12	Radiation	R	400 r					
			L	400 r					

7	8/22	Cortisone		300 mg., p. o.	Initial remission in 1 day; relapse after 1 wk. with final subsidence after irradiation 6 wk. later	17	—16	After 5 wk. thyroid biopsy "chronic thyroiditis, lymphatic type"; gland normal 3 mo. later	34 (11/10)
(F)	8/23			200 mg., p. o.					
	8/24–8/29			100 mg., p. o., o. d.					
	8/30–8/31			50 mg., p. o., o. d.					
	8/27–9/1	Corticotropin		40 units I. M., o.d.					
	9/21–9/28	Cortisone		100 mg., p. o., o. d.					
	9/29–10/5			50 mg., p. o., o. d.					
	10/5–10/19	Radiation	R	650 r					
			L	500 r					
8	8/29	Cortisone		300 mg., p. o., o. d.	Complete remission in 1 day; relapse after 2 wk. controlled by hydrocortisone after partial remission with irradiation	2	—4	Protracted course with thyroid biopsy "chronic thyroiditis, lymphatic type"; gland still slightly enlarged	16 (11/30)
(F)	8/30			200 mg., p. o., o. d.					
	8/31–9/4			100 mg., p. o., o. d.					
	9/5–9/7			50 mg., p. o., o. d.					
	9/8–9/10			25 mg., p. o., o. d.					
	9/7–9/10	Corticotropin		40 units I. M., o.d.					
	10/1–10/12	Radiation	R	400 r					
			L	400 r					
	11/1–11/22	Hydrocortisone		20 mg., p. o., o. d.					
		Thyroid extract		30 mg., p. o., o. d.					
9	11/20–11/28	Prednisone		15 mg., p. o., o. d.	Complete remission in 2 days	23	+8	Asymptomatic, thyroid normal	9 (3/1)
(F)	11/29–12/5			10 mg., p. o., o. d.					
	12/6–12/19			5 mg., p. o., o. d.					
10	8/8	Cortisone		300 mg., p. o., o. d.	Complete remission in 1 day, with the gland slightly enlarged for 1 mo.	43.8 (8/23)	—5 (8/21)	Biopsy revealed "subacute thyroiditis"; no further symptoms	4 (9/4)
(F)	8/9			200 mg., p. o., o. d.					
	8/10–8/18			100 mg., p. o., o. d.					
	8/19–8/21			50 mg., p. o., o. d.					
	8/17–8/24	Corticotropin		40 units I. M., o.d.					
	8/25–8/27			20 units I. M., o.d.					
11	6/23	Cortisone		300 mg., p. o., o. d.	Temperature became normal 1 day; all symptoms subsided by 5th day	25 (8/23)	+4 (8/23)	Thyroid normal	8 (8/23)
(F)	6/24			200 mg., p. o., o. d.					
	6/25–6/28			100 mg., p. o., o. d.					
	6/29–7/7			50 mg., p. o., o. d.					
12	12/12–12/21	Penicillin		300,000 units I. M., b. i. d.	Gradual decrease in all symptoms over 3-wk. period	None	None	Slightly enlarged tender thyroid persisted for month	13 (2/5)
(F)	12/11–12/22	Radiation	R	300 r					
			L	300 r					

cases. Ten required no further therapy after symptoms were controlled, but two had a protracted period of intermittent tender swelling of their thyroid glands for four and six months, respectively. In neither were the symptoms severe enough to instigate more than salicylate therapy. It is interesting to note that both of these patients underwent thyroid biopsy, but in both cases biopsy was performed because of the long duration of their disease and was probably not the cause of their prolonged discomfort. In nine the thyroid gland was no longer palpable within a month following termination of therapy, while in three the thyroid gland still remains slightly enlarged. These cases are summarized in the Table.

Comment

Acute nonsuppurative thyroiditis was first discussed by Ewald, in 1896. In 1936, de Quervain and Giordanengo [15] established the disease as an entity, and subsequently de Quervain's name was used as a synonym. Giordanengo [23] reviewed the literature from 1904 to 1938 and found a total of 54 cases, with many more being reported since that time.

Acute nonsuppurative thyroiditis has been known by many names during the last 50 years. The wide divergence of terms is probably based on the dispute as to etiology, but all seem to be associated with the same clinical disease. Subacute, acute recurrent, pseudotuberculous, tuberculous, sclerosing, struma granulomatosa, giant-cell, pseudogiant-cell of de Quervain, struma fibrosa-giant-cell variant, acute simple, acute noninfectious, and migratory thyroiditis are a few examples. Recently either acute nonsuppurative thyroiditis or subacute thyroiditis have been the preferred nomenclatures in an attempt to differentiate this disease from acute suppurative bacterial infections of the thyroid and the various forms of chronic thyroiditis.

The etiology of acute nonsuppurative thyroiditis is still a matter of dispute, although most thyroid specialists believe that a viral agent is the causative factor.[11,42,49,62] Measles,[5] scarlet fever,[28] and malaria [50] have been implicated, with case reports of acute nonsuppurative thyroiditis, following each of these diseases. In each of these cases and in other instances an allergic response to bacterial infection of another organ has been postulated because of the failure to isolate any bacteria from the damaged thyroid tissue.[7] The response to steroid and/or adrenocorticotropin therapy would seem to give tangential support to this theory. Recent experimental work in rabbits by Rose [47] and Witebsky [61] gives rise to the possibility of an autoimmune reaction as the etiology of chronic thyroiditis of the Hashimoto's type. Roitt et al.[46] have examined this possibility in human subjects and demonstrated the ability of patients with Hashimoto's struma to cause precipitation of the plasma of other similarly diseased patients but not the plasma of normal subjects or of those with thyrotoxicosis. These studies may well be applicable to a similar mechanism in acute nonsuppurative thyroiditis.

The finding of giant cells, pseudotubercles, and the close proximity to lymphatic drainage from the lung led some of the early European writers to consider the tubercle bacillus as the causative organism. Among other possibilities have been included dental caries and recent dental work.[4] Among infectious agents, a virus remains the best possibility, though only one report of a fairly well-established case of transmission of the disease has been noted.[36] Thus, whether this is a specific thyrotropic virus, as might be indicated by Westwater's [62] study in which eight cases were seen in a period of five months, and in my experience where four cases were seen in women living within a six-block area of New York in a period of one and one-half months, or if this is a tissue response to a nonspecific invading virus cannot be definitely established at this time. Success of various forms of therapy has been attributed to the possible inactivation of the

virus by irradiation [42] or a competition by thiouracil for the viral binding position in the thyroid cells.[20]

Pathologically, the gland presents as an enlarged, bulging, glistening, pale mass without adhesions to the surrounding tissue. The thin capsule is easily cut, revealing gray-white avascular firm tissue. Microscopically fibrosis with proliferation of the stroma is noted. The acini are decreased in size and number, with extravasation of their colloid and associated inflammatory reaction with many polymorphonuclear leukocytes. Histiocytes, giant cells, pseudotubercle formation, and phagocytosis are frequently demonstrated.[11,30] The break-down of the acini is thought to be due to viral invasion, and the tissue response is secondary to the release of thyroglobulin into the surrounding tissue, causing further follicle destruction and foreign-body reaction. This inflammatory picture has been responsible for the disagreement as to etiology and is the basis for most of the symptomology. It is believed that after about 10 days there is a round-cell infiltration and that the microscopic picture cannot then be differentiated from chronic thyroiditis. In the series reported in this paper two of the three biopsy specimens were thought to represent chronic thyroiditis, though the clinical course in neither resembled this disease. The European pathologists feel that most cases progress to chronic thyroiditis of the Riedel's type,[57] but most American authors disagree with this concept.[14,37,59]

The incidence as far as hospital admissions at St. Luke's is concerned is approximately 0.01%, which is misleading because of the often benign course of the disease and the probability that many cases are treated in the office of the private physician. Werner [59] feels that this disorder constitutes between 0.5% and 2.0% of all thyroid disease, while Lasser [38] believes the lower figure to be more accurate. In 1945, St. John [48] reviewed all cases of acute nonsuppurative thyroiditis at Duke and the Cleveland Clinics and found 40 and 38 cases, respectively, over a 10-year period. Crile [11] believes that the seeming increased incidence is due to a greater awareness and accuracy of clinical diagnosis. I believe that the more readily available laboratory techniques must receive some credit for this greater accuracy and apparent increased incidence.

Females are more commonly affected, with the ratio to males quoted as from a high of 7:1 [37] to 4:1 [41] or 2:1.[59] The age span is from 16 to 75 years, with the disease occurring most often in the fourth and fifth decades.[41] There does not appear to be any specific predeliction for a particular occupation, although, because of the prevalence in women, many of those afflicted are housewives.

Two types of acute nonsuppurative thyroiditis have been noted. This differentiation merely refers to speed of onset and is divided into the acute fulminating and the slowly progressive types.[10,45] They are similar as to pathology, subsequent course, and response to therapy. Preceding upper respiratory tract infection has been noted in from 25% [40,41] to 33%.[42] Most patients note approximately two weeks (occasionally up to three months) of vague nonspecific symptoms of malaise, fatigue, arthralgias, and anorexia, which is followed by the acute phase, with daily fever and chills, weakness, lassitude, and headache for approximately one week, which probably signifies the viremia. Subsequently, symptoms of localization and hypermetabolism supervene, with sore throat, dysphagia, cough, neck pain with characteristic radiation to an ear or rarely the teeth, and the appearance of a tender warm erythematous mass in the neck. The thyroid enlargement is bilateral in about two-thirds of the cases, with the remainder being approximately equally divided between unilateral and isthmic distribution. During the period of acinar destruction and colloid release, the patient complains of nervousness, weakness, tremor, palpitations, excessive diaphoresis, weight loss, heat intolerance, and emotional instability.[62] These symptoms subside within a

week, and then merely the neck pain and a tender thyroid mass remain from one to six months if no therapy is instituted.

The physical examination will vary with the phase of the disease from no findings early in the course to the more extensive signs of complete involvement of the thyroid gland. Elevation of the pulse rate to between 90 and 110 per minute, with a slight increase in the pulse pressure and a fine tremor of the hands, may be noted. There is a firm, tender, often warm and erythematous, enlarged thyroid which is easily moved and delineated from the surrounding tissues. The disease may involve one lobe at first in about 10% [59] or may involve one lobe and then extend or migrate to involve the remaining thyroid tissue. Many are mildly febrile for one or two weeks, but levels as high as 102 F [42] or 104 F [11,30] have been noted. The thyroid is usually enlarged to about twice its normal size and may remain enlarged for many months, with about 10% remaining enlarged indefinitely.

Laboratory studies reveal an elevation of the sedimentation rate to relatively high levels, 50 to 80 mm. (Wintrobe) in one hour,[59] in almost all cases, without a concomitant rise in the white blood cell count, which is usually between 7000 and 10,000, with a normal differential. The basal metabolism rate is usually moderately increased during the acute phase as a manifestation of the hypermetabolic state produced by tissue extravasation and subsequent blood stream absorption of the thyroglobulin. BMR values from −20 to +37 have been recorded, with the usual levels ranging from +10 to +15. A decrease in the serum albumin and an increase in α- and γ-globulins have been noted,[51,52,59] but insufficient determinations have been made to ascertain whether this is a specific response or merely a manifestation of an infectious process. Recently, Skillern, Nelson, and Crile [51] have called attention to the frequency of a mild normochromic normocytic anemia in some cases of acute nonsuppurative thyroiditis and postulate interference with bone marrow metabolism as the cause.

The protein-bound iodine seems to be elevated early in the course of the disease when more colloid is available, with values of 8.8μg. to 9.6μg. per 100 cc. being recorded.[14,31] As the thyroglobulin is dissipated, the PBI level falls and the thyroid-stimulating hormone mechanism recovers, with a return to normal levels in three to four weeks.[24]

The most useful diagnostic test for acute nonsuppurative thyroiditis is that of the RAI uptake or urinary excretion. The uptake is usually very low, with values between 0% and 10%, or an average of about 7%, while many levels are recorded in the 1% and 2% range.[11,20,24,30,39,43,45,54,59] This is due both to the destruction of the gland, rendering it unable to trap circulating iodine, and to the increased plasma levels of thyroxine, which cause a blockage of the TSH mechanism, eliminating the stimulus to RAI absorption by the thyroid gland.[14,43] These same factors explain the high urinary excretions of 80% to 90% of the administered iodine dose in 24 hours.[31,39] The RAI uptake values are low even in unilateral involvement, owing to the suppression of TSH secretion,[1] but normal values have been noted by Taylor [54] and Duncan [16] and in one of my patients, was confirmed by a triiodothyronine test.[60] The reason for these normal values is unexplained, and one can only suspect the presence of normal atopic thyroid tissue and sufficient TSH stimulation. Perhaps these normal values may be an indication that the patient was already in the rebound or recovery phase of the disease. The very low RAI uptake value helps in the establishment of the diagnosis of acute nonsuppurative thyroiditis versus Riedel's chronic thyroiditis, where the values are normal, and Hashimoto's chronic thyroiditis, where values are of low normal levels but do not approach the 10% and lower levels.[39]

Recently a modification of the RAI uptake with the use of TSH has helped in the diagnosis of borderline cases where there is asymptomatic thyroid enlargement with minimal febrile reaction. Robbins,[45] in 1951, showed that by giving large doses of TSH (30 mg.) for two to five days he could cause an increase in 5.8% to 34.8% in the RAI uptake. Jefferies,[27] Bishopric,[3] and Skillern [51] have shown that by the use of small doses (4 units [10 mg.]) of TSH they can differentiate acute nonsuppurative thyroiditis from normal controls and various other forms of thyroid disease. In 12 with acute nonsuppurative thyroiditis, 10 had no RAI uptake increase 24 hours later, while 2 had an increase of 7%. In 11 controls there was at least a 12% increase, while most increased by 25% or more.

The use of needle biopsy may occasionally be helpful, but because of the small specimen and distorted tissue with the early appearance of a chronic type cellular infiltration,[61] this procedure may be unrewarding. In the hands of experienced persons who see many such small tissue specimens, needle biopsy may be of diagnostic value [12,13] but my experience with three such cases was discouraging.

Differential diagnosis usually provides no problem if a careful history and physical examination are performed and the appropriate laboratory tests utilized. Upon first examining the patient the observer must consider a nodular goiter or thyroid cyst, with hemorrhage, pharyngitis, tonsillitis, upper respiratory tract infections, cervical adenitis, myositis, neuralgia, and cellulitis. Because of presenting symptoms of hypermetabolism, hyperthyroidism may be considered, and owing to the firmness of the gland, the diagnosis of carcinoma is often included. In confusion, teeth have been extracted and tonsils have been removed before the correct diagnosis was established.

The duration of the disease may be from one to eight months, with the acute illness from three days to three weeks and the febrile illness from one to eight weeks. The great majority of patients have a total course of four to eight weeks. Recurrence of symptoms occurs in from 10%-20%, depending on the type and duration of treatment.

Owing to the lack of knowledge as to etiology, treatment has been variable and apparent success of many measures must be attributed to the self-limited course of the disease. Nonspecific symptomologic therapy, with rest, analgesics, and local ice packs, should be used as needed to control pain, with stronger agents such as codeine being added when necessary.

Surgery has been employed both diagnostically and as therapy with full relief but occasional occurrence of hypothyroidism.[9,55] Biopsy alone was credited with cure in two cases of Campbell.[4] With the advent of antibiotics and often because of the suspicion of a bacterial etiology or at least secondary bacterial infection, these agents have been used. No definitely documented cases of successful treatment with penicillin, sulfonamides, or the broad-spectrum antibiotics have been published to date, while many failures, including some of my cases, are noted.[6,7,22,26,30,38,41,48,54,55] Such agents should be used only when definite evidence of thyroid suppuration or another form of bacterial infection is demonstrated, since secondary bacterial invasion in acute nonsuppurative thyroiditis does not seem to be a common occurrence. Arsphenamine has also been used in one case without effect.[48]

The first effective therapy to be used was a thiourea derivative. In 1945, King and Rosellini [32] used thiouracil in 11 patients, with relief of symptoms in 8 within one week. They reported only one failure, since one patient was finally diagnosed as having Graves' disease and the other had Hashimoto's struma on microscopic examination of the surgical specimen. The same year, St. John and Nicholson [48] reported failure in both patients they treated with thiouracil. Using the dosage of 200 mg.

t. i. d. for seven days, then 200 mg. b. i. d. for five weeks, Cantwell [6] reported subsidence of all symptoms in one day and return of the gland to normal size in six weeks. He felt that the mode of action was blockade of thyroxin liberation into the tissues and thus a decrease in local inflammation. Reveno,[44] in 1951, reported 3 cases; Westwater,[62] in 1952, reported 4 cases, and Clark,[7] in 1953, reported 8 of 10 cases successfully treated with thiouracil, with only 1 case, that of Westwater,[62] becoming myxedematous. Cutler,[14] in 1954, and Moldover,[41] in 1956, have each reported a single failure with propylthiouracil with subsequent remission when corticotropin was used. Fraser and Harrison [20] and Johannessen [29] have reported a total of four cases fully relieved of all signs and symptoms in 2 to 17 days on methylthiouracil. Robbins [45] has reported successful treatment of five of six patients with thyroid-stimulating hormone, but no other reports of this mode of therapy have appeared.

Radiotherapy in small doses has been advocated by many investigators,[2,7,8,11,42,48,49,54] with only one definite statement that a patient remained permanently hypothyroid following such therapy [41] and a few reports of transient hypothyroidism.[11,42] There is a wide variance of opinion as to the effectiveness of radiotherapy, from belief that it is very successful and may well actually inactivate the virus [42] to the feeling that probably no help is obtained from irradiation.[48] Some authors [2,54] advocate the use of irradiation only if steroid therapy fails, since they feel that the steroid merely acts as a suppressive agent. The statistics vary greatly, but there appears to be about a 15% to 30% recurrence rate after radiotherapy.[7,11,42] Many patients who fail to improve on one course of approximately 800 r in divided doses to both lobes of the gland will respond to a second course of 400 to 600 r.[11,42] The usual course of therapy and dose is from 750 r to 2000 r at a rate of 100 r to each side of the neck each day, with most patients responding initially to about 800 r. This form of therapy seems to be specific and effective, but as has been noted and confirmed in the series presented in this paper it is in those patients treated with irradiation that the symptoms of hypothyroidism are most often recorded. This, coupled with the relatively high recurrence rate, need of extensive hospital equipment for therapy, and the availability of other agents, would seem to indicate its use only when other forms of therapy have failed.

With the availability of the steroids and corticotropin a new approach to the treatment of acute nonsuppurative thyroiditis was established. The mechanisms of action of the steroid drugs may be numerous. They are well established as anti-inflammatory agents, and this may well be their sole mode of action in acute nonsuppurative thyroiditis. By decreasing the tissue response and thus irritative phenomena they can control symptoms during the natural course of the disease. If acute nonsuppurative thyroiditis is an allergic or antibody-antigen type tissue response localized in the thyroid, then here again steroids can find rational use as active suppressive agents. It is possible that the adrenal hormones are effective in yet another manner, since both the adrenal and the thyroid are stimulated by the pituitary and inter-reaction between the two glands is known to occur and has been partially established. Both steroids and corticotropin are able to suppress thyroid activity by pituitary inhibition as measured by RAI uptake.[43] In hyperthyroidism both steroids and corticotropin are capable of decreasing thyroid activity.[25] The RAI uptake is similarly depressed after stress or epinephrine, but in all cases the decrease in uptake is not accompanied by a decrease in thyroxine release.[25,43] The decrease in measurable thyroxine in the gland would seem to indicate a mechanism beyond that of TSH inhibition, probably a direct action on the gland. This increased release of thyroxine would block TSH and subsequent thyroid

gland stimulation. To substantiate this hypothesis, it has been shown that administration of corticotropin or steroids with TSH has no effect on RAI uptake or urinary excretion.[35] Kuhl and Ziff[35] have alluded to the possibility of such results merely being secondary to the calorigenic effect of steroids, while Fredrickson et al.[21] postulated an extrathyroidal fixation of iodine or an increased iodine excretion through a primary renal mechanism of the steroids.

From this information one can only surmise that, aside from their anti-inflammatory action, steroids or corticotropin may well act directly on the thyroid gland to bind thyroxin that has been extravasated into the tissues and further inhibit the TSH mechanism, giving the acini sufficient time to heal and retain thyroglobulin. Many reports of successful use of steroids have appeared in the literature during the last five years,[2,7,22,26,30,33,34,36,38,41,53-55,58,59] while other workers have used corticotropin alone[14,58] or in combination with steroids.[53,54]

In using corticotropin the best dosage schedule seems to be to start with 80 units a day and reduce the dose every other day by 20 units unless there is a return of symptoms. With cortisone, 300 mg. the first day, 200 mg. the second day, and then 100 mg. per day for a week with subsequent reduction of 25 mg. every other day, once again regulated by the patient's comfort, is the best regimen. Werner[58] found that there was a more rapid favorable response to corticotropin than to steroids, and there have been no reports of even transient symptoms of hypothyroidism. Benjamin[2] feels that if a patient "escapes" on steroid therapy he should receive irradiation, but I agree with Moldover[41] that sufficient steroid dosage for an adequate period of time without reluctance to increase the dose as needed is the most desirable form of therapy in acute nonsuppurative thyroiditis. In comparable dosage, prednisone can be used in place of cortisone with equal effectiveness. Owing to the apparently diminished number of undesirable side-effects, this agent is probably preferable. As in all cases of steroid therapy the physician must continually observe his patient for iatrogenic hyperadrenalism and, in prolonged use, guard against temporary adrenal hypofunction with corticotropin as steroids are withdrawn.

Barr,[1] in 1953, held that there were no cases of established myxedema following acute nonsuppurative thyroiditis, and certainly most available reports seem to indicate that this is true.[10,11,37,49,57] Follow-up of all reported cases has failed to reveal more than one case of permanent hypothyroidism presumed to be from irradiation[41] and one from thiouracil.[57] The mild symptoms of hypothyroidism that rarely occur can usually be treated easily by small doses of thyroid extract or some of the newer triiodothyronine agents for a few weeks until the gland is sufficiently regenerated to produce its own thyroglobulin in adequate quantities. As noted before, most of the cases of transient hypothyroidism follow radiation therapy, and thus more discriminating use of this agent may further decrease the occurrence of these undesirable complications.

Summary

Acute nonsuppurative thyroiditis is a self-limiting disease of unknown etiology, possibly viral, usually lasting for one or two months. Occasionally a case may progress to a form of chronic thyroiditis, but the complication of permanent hypothyroidism is extremely rare. Use of steroids and/or corticotropin (ACTH) would seem to be the most efficacious and physiologic form of therapy at the present time. Variable results have been obtained with other forms of therapy, such as irradiation and the antithyroid drugs.

The compilation of the data of 12 previously unreported cases of acute nonsuppurative thyroiditis and a review of the literature are presented.

Drs. Edward Childs, Albert Herring, William Pyles, and Myron Wright gave permission for use of the case records of their patients.

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Addendum

Since preparation of the original manuscript two notable advances have been made toward further elucidation of the etiology of acute nonsuppurative thyroiditis. Eylan et. al.[18] demonstrated positive complement-fixation antibodies against mumps virus in 10 of 11 patients studied by them, while Felix-Davis[19] found a positive mumps virus hemagglutinin test in four patients with acute nonsuppurative thyroiditis.

The most significant advancement has been the continued interest of the immunologists in the field of thyroid disease.[17] They have extended their previously noted studies[46,47,61] to include all types of thyroid disease, and a recent report[19] revealed the demonstration of precipitin type antibodies to purified human thyroglobulin in a case of acute nonsuppurative thyroiditis. This extends the phenomenon of autoimmunization to another phase of thyroid disease. An even more striking implication is the demonstration of a self-limiting form of an autoimmune disease.

Probably the mumps virus is not a specific etiologic agent but rather one of many that cause injury to the acini, with release of the thyroglobulin into the surrounding tissues. As postulated in a recent editorial in *The Lancet*,[17] the bodily defenses respond to this "foreign" protein in an immunological manner because, while part of the body, it has been protected from internal environment and thus treated as an "unrecognized" substance. Any agent causing a release of the thyroglobulin into the tissues might start such a chain of events, resulting in the entity we know as acute nonsuppurative thyroiditis.

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Diagnostic Aspects of Subacute Bacterial Endocarditis in the Elderly

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As recently as 1940 it was authoritatively stated that the vast majority of cases of subacute bacterial endocarditis occur in patients younger than 50 years of age.[1] In a recent survey of the literature this was proven erroneous. From 10% to 50% of cases in the several series reviewed by Wallach et al. occurred in persons over 50.[2] Studies of postmortem material have given similar figures. In 94 cases of subacute bacterial endocarditis autopsied by Traut et al., 38% were in patients over 45 years of age. Cases have been reported in patients of all ages up to the 10th decade.[4]

Subacute bacterial endocarditis usually occurs in persons with diseased hearts, and since more such people for various reasons are living to old age, a greater frequency of subacute bacterial endocarditis in the elderly can be expected in the future. It is worth while to stress the occurrence of the disease in the elderly because in this age group it is frequently atypical and easily overlooked.[5] The success of modern antibiotic therapy for the disease is an added incentive to diagnose it correctly.

So far as the cardiac pathology is concerned, there is no remarkable difference between the disease in youth and in the elderly. Just as in younger patients, chronic rheumatic valvulitis is the commonest nidus for subacute bacterial endocarditis in the aged. In the series of 28 patients over 40 years of age reported by Bayles and Lewis, 16 had rheumatic heart disease, 7 had arteriosclerotic heart disease, 2 had syphilitic heart disease, and 3 had congenitally bicuspid aortic valves.[6] It is of interest that arteriosclerotic heart disease has been reported by others as a predisposing cardiac disease for subacute bacterial endocarditis.[7,8] The viridans Streptococcus is also in the elderly the commonest infecting organism. Dental extractions and skin infections are common portals of entry in the elderly as in younger patients. Genitourinary manipulations, such as cystoscopy, in the elderly have been cited as precipitating events in a number of cases.[9]

As regards the general clinical picture, however, the disease as it occurs in the elderly is much more often atypical than in younger patients.

Zeman classified his 18 cases of subacute bacterial endocarditis in the elderly according to the diagnostic problem presented. Nine showed typical clinical features, although these were modified by the effects of age. The correct diagnosis was not always made because of confusion due to other pathologic processes coincidentally present. Five cases had sterile blood cultures and were serious diagnostic problems. In four cases the diagnosis was completely obscured and missed.[4]

Report of Cases

The present material consists of 10 cases of subacute bacterial endocarditis in patients over 55 years of age seen consecutively at this hospital in the past decade. In each of these, the primary cardiac lesion was rheumatic and the infecting organism was the viridans Streptococcus. Ages of the patients varied from 57 to 81, and there were six men and four women.

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Of the ten, three showed typical clinical features of subacute bacterial endocarditis, with a heart murmur, fever, leukocytosis, splenomegaly, anemia, weight loss, and embolic phenomenon. They are not abstracted here.

The remaining seven cases were difficult diagnostic problems, and the diagnosis was made in only three of these. Three of the seven cases presented as major psychoses, and one each, as gastrointestinal disease, renal insufficiency, simple wasting, and apoplexy in a hypertensive person.

CASE 1.—An 81-year-old white man was referred to the hospital because he had suddenly become confused, noisy, and belligerent and had threatened to kill his wife. After he was subdued by police he was brought to the hospital by ambulance and put in a locked room in the psychiatric ward. The symptoms had evidently begun very suddenly, and he had previously been well following a minor operation 10 months before. Examination showed carious teeth, a harsh systolic apical murmur, a temperature of 99.5 F by mouth, and no other physical abnormalities.

His mental state continued confused and paranoic. Occasionally his temperature was as high as 100.0 F, but never higher. His hemoglobin level was 11.0 gm. %, and there was an elevation of the blood urea nitrogen to 60 mg. %. Six weeks following admission, after a progressive downhill course in which he simply grew weaker, he died in a coma.

Postmortem examination showed chronic rheumatic mitral valvulitis, with subacute bacterial endocarditis. The brain was not examined.

In summary, this patient showed confusion, delirium, and paranoid ideas, with progressive weakness, occasional slight temperature elevations, and a systolic apical murmur, and died in coma. Subacute bacterial endocarditis was found at autopsy.

CASE 2. —A 68-year-old white woman was admitted in a confused mental state, disoriented, delirious, and agitated. Her family reported she had shown easy forgetfulness, insomnia, and childish behavior for the past two or three years, with a relatively sudden onset of the delirious state in the week before admission. Examination showed a spare, tense, confused white woman, babbling disjointed meaningless phrases. The temperature was 102.0 F, with a rapid irregular pulse. There was a blowing apical systolic murmur, with no other abnormal findings on physical examination. Routine laboratory studies showed a normal blood cell count and urinalysis, normal chest x-ray, and atrial fibrillation on the electrocardiogram. Blood cultures were sterile. Five days after admission she suddenly became comatose and died.

Postmortem examination showed multiple cerebral emboli, with old and recent infarcts of the brain. There was chronic rheumatic mitral valvulitis and subacute bacterial endocarditis with vegetations on the mitral valve.

In summary, this patient showed what appeared to be a senile delirium engrafted on a mild senile psychosis, with a heart murmur, fever, and sterile blood cultures. Postmortem examination showed multiple cerebral emboli due to subacute bacterial endocarditis.

CASE 3.—A 67-year-old white man was admitted because of weight loss and depression. On admission, he was very depressed and uncommunicative. From his family it was learned that he had suffered occasional periods of moodiness in the past, but such periods were always short in duration, with spontaneous clearing. The present episode had commenced about two months before admission, with insomnia and anorexia. He had lost 15 lb. and had complained of dizziness, headaches, constipation, furred tongue, and abdominal bloating. In the two weeks before admission he had not stirred out of his room and had spent his time gazing at the wall.

Examination showed normal findings except for a faint apical systolic murmur. His temperature was 99.0 to 100.0 F daily. Laboratory studies showed a hemoglobin of 10.5 gm. %, with a white cell count of 12,500 and a normal differential. The chest x-ray, electrocardiogram, and blood urea nitrogen were normal; there was reversal of the albumin-globulin ratio.

A psychiatric consultant diagnosed involutional melancholia, but because of the low-grade fever and anemia several blood cultures were done, all showing a viridans Streptococcus. Treatment with penicillin resulted in a disappearance of his depression and fever, and in the six years since there has been no recurrence of either.

In summary, this patient showed classical symptoms of involutional melancholia, which cleared when his subacute bacterial endocarditis was adequately treated.

A number of workers have emphasized psychoses as presenting symptoms in subacute bacterial endocarditis.[10,11] The symptoms can be ascribed to focal encephalitis due to cerebral reaction to multiple small emobli or in some cases to gross infarctions. With cerebral vascular changes of aging

already present, it would be expected that such symptoms might be more readily produced in the elderly patient.

CASE 4.—A 68-year-old white man was admitted following a four-month period of anorexia and a feeling of fullness in the abdomen after eating small amounts of food. He had developed irregular bowel habits, with alternating constipation and diarrhea. There was occasional vomiting, especially if he tried to eat solid food, and because of this he had subsisted on milk and other liquids. There had been a loss of 20 lb. in the previous six months, and he complained of frequent cramp-like lower abdominal pain, usually relieved by a bowel movement.

Physical examination showed slight hepatomegaly, slight splenomegaly, a low-grade fever, and a moderately loud blowing apical systolic murmur. Laboratory studies showed a hemoglobin of 10.5 gm. %; a white cell count of 7500, with a normal differential; a serum bilirubin of 2.0 mg. %, and a total protein of 7.0 gm. %, with 2.8 gm. of albumin and 4.2 gm. of globulin. The prothrombin time was 47% of normal, and the sulfobromophthalein (Bromsulphalein) retention was 15% in 30 minutes with a dose of 5 mg. of the dye per kilogram. of body weight. X-ray examination of the stomach and duodenum was normal, and the barium enema showed diverticulosis.

A diagnosis of chronic hepatitis was entertained, but blood cultures done because of the murmur, fever, and anemia showed a viridans Streptococcus. Treatment with penicillin and streptomycin resulted in a disappearance of all symptoms.

In summary, this patient showed signs, symptoms, and laboratory findings indicative of liver disease, which disappeared with treatment of his subacute bacterial endocarditis.

The liver as a focal point of symptomatology in subacute bacterial endocarditis was emphasized by Traut and co-workers in their study of the disease in elderly people because of the frequent occurrence of hepatomegaly.[3] Alteration of the serum protein pattern is common. Focal necrosis of liver cells with surrounding polymorphonuclear infiltration, presumably due to emboli, has been noted, and chronic passive congestion may occur if the patient is in heart failure.[12]

CASE 5.—A 69-year-old white man was admitted because of weakness, pallor, and weight loss. Two months previously a blood urea nitrogen level of 35 mg. % had been found in the clinic. He had been attending the clinic regularly following a transurethral resection for benign prostatic hypertrophy, which had been performed one year previously. He complained on admission of anorexia, weight loss, weakness, and ankle swelling.

Physical examination revealed emaciation, a uremic odor to the breath, a hemoglobin of 9.0 gm. %, and a white cell count of 16,200, with 80% polymorphonuclear cells and 20% lymphocytes and many clumps of white cells in the urinary sediment. There were Escherichia coli on urine culture, a normal chest x-ray, and a blood urea nitrogen of 110 mg. %.

In the hospital he became progressively weaker. No fever was ever recorded, and no petechiae were found on numerous physical examinations. Two weeks after admission a blood urea nitrogen was 180 mg. %, and two days later he died in a coma.

Postmortem examination showed chronic rheumatic mitral valvulitis and the vegetations of subacute bacterial endocarditis. The kidneys were slightly enlarged, with pitted granular surfaces. There were multiple areas of renal infarction. Microscopic sections showed a diffuse glomerulitis as well as pyelonephritis.

In summary, this elderly man developed progressive uremia which clinically appeared to be due to resistant E. coli pyelonephritis. At postmortem examination subacute bacterial endocarditis was discovered, with diffuse glomerulitis the major finding in the kidneys.

The kidneys are the second most frequent sites of embolic phenomena in subacute bacterial endocarditis. In addition, a significant percentage of cases of the disease show a diffuse glomerulonephritis.[13] It has been reported that progressive renal failure is especially likely to occur in cases of subacute bacterial endocarditis with sterile blood cultures.[14]

CASE 6.—A white man was first seen at the age of 64, complaining of weakness and weight loss. There were no complaints referable to any specific body system, but the patient reported he simply had lost his appetite, could not eat, and thus had lost weight. There was no serious illness in his past history except for a subtotal gastric resection for bleeding duodenal ulcer.

Physical examination showed emaciation and two tender bluish swellings over the dorsum of the left foot. There was a faint blowing apical systolic murmur. Laboratory studies showed a hemoglobin of 10.9 gm. %, with 7900 white cells per cubic millimeter and a normal differential. The

basal metabolic rate was plus 29%, and the total protein was 6.0 gm. %, with 2.8 gm. of albumin and 3.2 gm. of globulin.

Examination of the chest and the gastrointestinal tract by x-ray showed no significant abnormalities, and an electrocardiogram was normal.

Under daily observation for six weeks the patient had no oral temperature greater than 99.0 F, with a maximal diurnal variation of 2.5 degrees (F). Progressive anemia and wasting, with the faint heart murmur, led to the performance of several blood cultures, all of which grew out a viridans Streptococcus. Under two weeks of treatment with penicillin and streptomycin he regained his weight and strength, the anemia disappeared, and he returned to work. The temperature was never over 99.0 F by mouth.

In summary, this elderly man complained of anorexia and weight loss and had a heart murmur. Blood cultures showed subacute bacterial endocarditis, which was cleared with treatment, with resultant improvement in appetite and weight gain and return of strength. During six weeks of observation before treatment he never had fever.

While fever is an almost constant feature in subacute bacterial endocarditis, the normally low body temperature of an elderly person may result in confusion. This patient may actually have had "fever" with a temperature of 99.0 F if his normal body temperature was 97.0 or 97.5 F. Another possible explanation of the failure to find a temperature higher than 99.0 F in this patient may have been that he was in a prolonged afebrile phase of the disease during our period of observation. Such periods have been reported to last as long as two or three months.[15]

CASE 7.—A 60-year-od white woman was admitted in coma. She had been in fairly good general health until an hour before admission, when she had suddenly collapsed in her room, developed a generalized convulsion lasting several minutes, and lapsed into a deep stupor. Examination showed hypertension, with a blood pressure of 180 systolic and 110 diastolic, a stiff neck, and aortic systolic and diastolic murmurs. The Babinski sign was bilaterally positive. A spinal tap revealed grossly bloody fluid with a pressure of 30 mm. of water.

The patient remained in coma and steadily grew weaker. There was a low-grade fever, ranging from 100.0 to 102.0 F rectally, and occasional generalized convulsions occurred. Laboratory studies showed a hemoglobin of 12.8 gm. % and a white cell count of 16,500, with 85 polymorphonuclear cells and 15 lymphocytes. The blood urea nitrogen was 50 mg. %, and the total protein was 6.8 gm. %, with 3.0 gm. of albumin and 3.8 gm. of globulin. Blood cultures done on the second and third days of hospitalization were sterile. She died in coma seven days after admission, never having regained consciousness.

At autopsy, there was rheumatic mitral and aortic stenosis and insufficiency, with the vegetations of subacute bacterial endocarditis on both valves. There was a massive cerebral hemorrhage due to embolism of the left middle cerebral artery. There were several small old cerebral infarcts.

In summary, this elderly hypertensive woman sustained a cerebral hemorrhage and subsequently died in coma. At postmortem examination subacute bacterial endocarditis was found to have produced the cerebral lesion rather than hypertensive cardiovascular disease.

Clinical signs and symptoms of central nervous system disease in subacute bacterial endocarditis are frequent, and their sudden dramatic onset may be the presenting problem, as in this case. Toone emphasized the frequency with which cases of subacute bacterial endocarditis are seen on neurological services.[16] Cerebral infarcts, large and small, subarachnoid hemorrhage, or a diffuse embolic encephalitis may occur singly or in combination.[17]

Comment

It is agreed that the clinical picture of subacute bacterial endocarditis in the elderly is often confusing and atypical.[4-6] Those clinical events so striking in the young are often not so obvious in the elderly. A slight heart murmur is easily passed off as being due to arteriosclerotic heart disease, and a low-grade fever, as being due to a "patch of bronchopneumonia." The chief obstacle to diagnosis of the disease in the elderly is the common occurrence of a variety of pathological processes of differing etiology in the same person and the difficulty in distinguishing the clinically most significant

findings. The disease often seems simply to accentuate previously present pathological processes, and it is easy to assume the accentuation to be due to advancement of the originally present process rather than due to a new additional disease.

This series of 10 consecutive cases of subacute bacterial endocarditis seen at this hospital in patients over 55 years of age is noteworthy in that only 3 of the group showed the clinical picture commonly associated with the disease. This high incidence of atypical cases is characteristic of the disease in old people.

Helpful in making the diagnosis is the presence of a heart murmur, which was noted on physical examination in all of these patients. Also, when it was measured, the serum protein pattern always showed reversal of the albumin-globulin ratio. However, no other single clinical sign or symptom was present in all these patients. It might well be said that the presence of a heart murmur should be a reminder of the possibility of the disease in any elderly patient, even if the rest of the clinical picture would seem to suggest the presence of a psychosis, renal insufficiency, a gastrointestinal malignancy, or other unconnected illness.

Summary and Conclusions

Ten consecutive occurring cases of subacute bacterial endocarditis seen at this hospital in elderly patients are reported.

Of these 10, only 3 showed the typical clinical picture of the disease. Three cases presented as psychoses, and one each, as gastrointestinal disease, renal insufficiency, apoplexy, and simple weight loss without fever.

Subacute bacterial endocarditis as it occurs in the elderly is usually atypical. The only clinical sign or symptom constantly present in this series was a heart murmur.

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Sarcoidosis

Clinical Observation on One Hundred Sixty Cases

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Sarcoidosis can no longer be regarded as a rare disease. A recent investigation disclosed 1194 cases of this disease in Veterans' Administration Hospitals in a five-year interval,[1] and chest x-ray surveys of 1,000,000 inhabitants of Sweden between 1950 and 1954 detected almost half as many cases of sarcoidosis as of tuberculosis.[2] Whether these impressive numbers of cases are merely the result of better recognition or whether sarcoidosis is actually increasing in prevalence remains to be determined. In either event, because of its growing importance, sarcoidosis is a disease with which all physicians should be familiar.

Reported here are observations in 160 patients who came under our observation between 1938 and 1956, in clinic, hospital, or office practice. All cases included in this series had one or more biopsies demonstrating epithelioid tubercles.

The age and sex distribution of these patients, shown in Table 1, is typical of that observed in other studies made in large eastern cities.[3,4] Although Negroes predominate in all such studies, it should be noted that there were only 9 Negroes among 194 cases of sarcoidosis observed at the Mayo Clinic.[5] The higher prevalence among females is another noteworthy fact that must be taken into consideration in attempts to ascertain the etiology of this disease by epidemiological study.

Some of the most interesting reports on sarcoidosis in this country have been those which described a predominance of this disease among persons born in the southeastern states. The birthplace data presented in Table 2 appear at first glance to substantiate the observations of Michaels and his associates.[6] However, a comparison with tuberculous patients similar in economic circumstances suggests that this geographic distribution is characteristic of Philadelphia dispensary patients rather than of sarcoido-

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TABLE 1.—*Age and Sex Distribution of 160 Patients with Sarcoidosis*

Age	Negro	White
Under 21	23	2
21-30	80	8
31-40	28	7
Over 40	7	5
Negro: Range 9 to 53 yr.; mean 26.9 yr.		
White: Range 13 to 62 yr.: mean 32.5 yr.		
Sex	**Negro**	**White**
Male	44	11
Female	94	11

TABLE 2.—*Birthplace of 159 Patients with Sarcoidosis and 200 Control Subjects with Tuberculosis* *

	Sarcoidosis		Tuberculosis	
	Negro	White	Negro	White
Pennsylvania	23	14	39	29
Other northern states	6	4	5	2
Southeastern states	107	1	112	0
Europe	0	3	0	11
Other	1	0	2	0
Total	137	22	158	42

* Two hundred consecutive cases with diagnosis of tuberculosis at the Henry Phipps Institute in 1951.

sis patients alone. Our findings neither support nor weaken the observations which have been made concerning the geographic distribution of sarcoidosis.

General Features

Clinical Features.—The manifestations of sarcoidosis are often insidious, and the disease is frequently discovered by mass x-ray surveys rather than because the patient is impelled by symptoms to seek medical care. This should not be interpreted to indicate that patients with sarcoidosis suffer no impairment of health. As Table 3 shows, most patients with sarcoidosis do have symptoms, and these may be extremely severe. Only 11% were truly free of complaints. The commonest symptoms were systemic ones, such as weight loss and fatigue, which may be due to the hepatic involvement that is so common in sarcoidosis. Next in frequency, as might be expected, are respiratory symptoms, such as cough, dyspnea, and chest pain.

TABLE 3.—*Frequency of Systemic and Respiratory Symptoms in 160 Patients with Sarcoidosis*

	Percentage with Symptoms
Weight loss	54
Fatigue	44
Joint and muscle pain	9
Fever	6
Cough	51
Breathlessness	39
Chest pain	29
Hemoptysis	7
No symptoms	11

The relative frequency of involvement of various systems or organs is influenced by the type of clinical material studied, and varies widely in different series. The early interest of dermatologists in this disease was reflected in the frequency with which cutaneous lesions were described in reports some years ago. Similarly, a hospital with an eye clinic with keen interest in saracoidosis will have a high proportion of ocular cases. It is believed that the data shown in Table 4 are not biased in this fashion and are in general representative of the frequency with which various lesions are clinically encountered.

TABLE 4.—*Frequency of Common Abnormalities Detected on Physical Examination of 160 Patients with Sarcoidosis*

	Percentage
Peripheral adenopathy	69
Cutaneous sarcoids (45 patients) / Erythema nodosum (3 patients)	30
Hepatomegaly	19
Splenomegaly	15
Ocular lesions (23 patients) / Lacrimal gland enlargement (5 patients)	18
Parotid enlargement	6
Negative examination	13

Abnormal physical findings are not marked in the majority of patients with sarcoidosis. Although lymphadenopathy is common, it is often slight, and may be localized to one or two axillary or inguinal nodes. Involvement of the lacrimal or salivary glands is relatively infrequent. Examination of the chest, except in advanced cases with secondary emphysema, is usually normal, and cardiac auscultation is in most instances negative. Hepatomegaly and splenomegaly are, aside from the ocular and cutaneous changes, the most frequent signs.

The frequency of the less common manifestations of sarcoidosis is indicated in Table 5. Recognition of these syndromes is important, and their characteristics will be more fully discussed subsequently.

Laboratory Features.—The common laboratory studies are not greatly abnormal. Changes in the erythrocyte count or hemo-

TABLE 5.—*Frequency of Less Common Manifestations in 160 Patients with Sarcoidosis*

	Number
Heart	
Myocardial sarcoidosis	1
Cor pulmonale	3
Both	2
Pleura (nontuberculous effusion)	3
Kidneys	2
Larynx and nasopharynx	1
Thrombocytopenic purpura	2
Central nervous system	2
Seventh cranial nerve	3
Pituitary gland	2
Hypercalcemia and renal stone	2

globin are rarely marked. The white cell count is infrequently elevated and is usually low (Table 6). White cell counts below 5000 occurred in 37.5% of our cases. Eosinophilia (count more than 4%) was observed in 21.8%.

Serum Calcium.—Elevation of serum calcium has been reported, with a frequency ranging from 3% to 20%. The elevated calcium levels are not associated with osseous involvement: Hypercalcemia has been noted both with and without bone changes. The hypercalcemia does not appear related to the serum protein alterations. Elevation of alkaline phosphatase concentration in the serum has been observed frequently, but is poorly correlated with manifest bone changes, and is more probably the result of hepatic dysfunction.[18]

Serum Proteins.—Hyperglobulinemia is one of the commonest abnormalities observed in patients with sarcoidosis. Despite the fact that methods employed in routine laboratories in the past for fractionation have precipitated a portion of the globulin with the albumin, abnormal values of globulin of 3.0 gm. or more were observed in 68% of Riley's cases [4] and values greater than 3.5 gm. occurred in 45.6% of our patients (Table 6). The recent employment of more specific methods reveals an even greater frequency of globulin elevation. Use of the Kunkel test and electrophoretic methods indicate that the γ-globulin fraction is most frequently and most markedly increased.

The Tuberculin Reaction.—It is a striking fact that patients with sarcoidosis in Scandinavia, England, Continental Europe, and the United States react similarly to tuberculin, even though the frequency of reactions among the general populations of these countries varies considerably. Two-thirds of patients with sarcoidosis fail to react to conventional second-strength doses (0.005 mg. PPD, or 1.0 mg. OT). A reaction to first-strength tuberculin is exhibited by approximately 5% of patients with sarcoidosis, and about 25% react to second-strength tuberculin (Table 7). When a reaction to first-strength tuberculin is manifested, special consideration should be given the possibility that tuberculosis has simulated or superinfected sarcoidosis.

TABLE 6.—*Blood Tests in Patients with Sarcoidosis*

	Percentage
Serum protein levels (103 patients)	
Serum globulin greather than 3.5 gm	45.6
Total protein greater than 8.0 gm	20.6
White blood cell count (144 patients)	
2501-5000	37.5
5001-10,000	60.4
10,001-15,000	2.1
Eosinophil percentage (133 patients)	
0-3	78.2
4-7	17.3
More than 7	4.5

TABLE 7.—*Tuberculin Tests in Patients with Sarcoidosis*

Tuberculin reaction (156 patients with complete tests)	Percentage
Positive to 0.00002 mg. PPD	6.4
Positive to 0.005 mg. PPD	22.0
Negative to 0.005 mg. PPD	71.6

Sarcoidosis of the Respiratory System

Roentgenological evidence of pulmonary or tracheobronchial lymph node involvement is observed in 95% of patients with sarcoidosis, and death from respiratory insufficiency due to progressive pulmonary damage is the commonest cause of death in this disease.

The frequency and the severity of the pulmonary changes have been interpreted as evidence that sarcoidosis is primarily a respiratory infection. Gendel and his associates,[7] on the other hand, have pointed out that mediastinal lymph node enlargement precedes the pulmonary infiltration, and these observations are confirmed by the data in Table 8.

The pattern of pulmonary infiltration as observed by roentgenologic examination may take various forms. Disseminated miliary or nodular foci, resembling hematogenous tuberculosis, are probably the earliest lesions. Commoner are the diffuse linear infiltrations extending outward from the hili, and

TABLE 8.—*Findings on Chest Roentgenogram: of 160 Patients with Sarcoidosis*

Findings on Initial Examination	No. of Patients	No. Subsequently Developing Infiltration	No. Subsequently Developing Adenopathy
Negative	9	0	0
Mediastinal adenopathy	54	17	--
Infiltration alone	42	--	0
Adenopathy and infiltration	55	--	--

resembling lymphangitic carcinomatosis. Denser and larger bands of infiltration, appearing fibrotic in character, and resembling silicosis, are occasionally observed. Scattered patches of increased density, resembling pneumonitis, are more frequently seen. The pulmonary lesions of sarcoidosis are almost always bilateral, and usually symmetrical. Unilateral lesions are rare; we have encountered only one such case satisfactorily proved.

The mediastinal lymph node enlargement is also, with rare exceptions, bilateral. The nodes are occasionally greatly enlarged and sharply defined, giving the appearance described as "potato" nodes. In contrast to the adenopathy of tuberculosis and lymphomas, the nodes of sarcoidosis rarely narrow or occlude the bronchi which they surround. Atelectasis due to compression of bronchi by sarcoid nodes has, however, occasionally been described.[7] Involvement of the recurrent laryngeal nerve has been reported, but not of the phrenic nerve. The mediastinal lymphadenopathy often persists for years, but occasionally clears completely within a few months.

The patterns of involvement of other portions of the respiratory tract are interesting. Involvement of the nasal mucosa is not infrequent, while sarcoidosis of the larynx has occurred in only one case in our series. The bronchial mucosa is more frequently involved, and numerous instances have been reported in which biopsies of bronchial mucosa provided histologic evidence of sarcoidosis.[8] The rarity with which sarcoidosis involves serous membranes has been emphasized. Convincing evidence of instances of pleural sarcoidosis have not been reported; this is the more remarkable because of the frequency with which the underlying lung is involved.

Sarcoidosis of the Cardiovascular System

Sarcoidosis of the pericardium, aorta, or peripheral vessels has not been reported. Involvement of the myocardium is not uncommon, usually occurring in severe generalized forms of the disease. Occasionally, however, severe cardiac infiltration may occur with little or no clinical evidence of disease elsewhere. Stephen[9] has reported the case of a 47-year-old white man whose history and electrocardiograms were indicative of acute myocardial infarction. Discharged after a month's rest in the hospital, the patient suddenly died two weeks later, and necropsy revealed extensive myocardial sarcoidosis with scattered sarcoid tubercles in the lungs and mediastinal nodes. Sudden death is not rare as the result of myocardial sarcoidosis; this occurred in 5 of 11 cases described by Gilg.[10]

The commonest manifestation of myocardial sarcoidosis is congestive failure. Gilg observed this in five cases, and we have encountered three instances, all responding in striking fashion to the administration of cortisone. The Stokes-Adams syndrome is another manifestation of sarcoidosis of the heart which is not infrequent.[11]

Ocular Sarcoidosis

Estimates of the frequency of ocular involvement in sarcoidosis range widely. It is probable that symptomatic lesions are not often overlooked, but less obvious ones are detectable only by slit-lamp examination, and will not be recognized unless special interest exists in the subject of ocular sarcoidosis. Such special interest at The Johns Hopkins Hospital has resulted in demonstration of ocular lesions in 60% of patients with sarcoidosis.[3] In most series, however, ocular

involvement is described in only 25% to 30% of patients.[12]

Sarcoidosis may affect the lacrimal glands, conjunctiva, sclera, and the iris and uveal tract, or rarely the retina.

Pain is seldom noted; difficulty in vision or discomfort, giving the sensation of a foreign body, is more commonly the complaint of patients with symptomatic lesions. It is to be emphasized that the ocular lesions are not specifically characteristic of sarcoidosis. Sarcoidosis and tuberculosis cannot be differentiated by ophthalmological examination.

Sarcoidosis of the Nervous System

Seventh cranial nerve paresis is a frequent manifestation of sarcoidosis, especially in cases with parotid involvement. Palsies of other cranial nerves and of peripheral nerves are less common. Central nervous system manifestations are not infrequent and may assume a wide variety of clinical guises. Intracranial tumor, meningitis, disseminated sclerosis, and cord tumor may be simulated, depending on the distribution and number of the sarcoid lesions.[13] In a patient with systemic sarcoidosis it is wise to attribute bizarre neurologic symptoms to central nervous system invasion by sarcoidosis.

Musculoskeletal Sarcoidosis

Sarcoidosis may be manifested principally by arthralgia and myalgia; these symptoms are frequently accompanied by erythema nodosum and fever, so that rheumatic fever naturally receives consideration. Myers and his associates[14] have emphasized the value of muscle biopsy in this syndrome: Gastrocnemius biopsy in several instances demonstrated sarcoid tubercles.

We have found muscle biopsy a useful means of demonstrating sarcoid lesions in patients with muscular and articular symptoms. Muscle biopsy has rarely been fruitful, however, in patients with sarcoidosis who do not have symptoms referable to these tissues.

Skeletal muscle sarcoidosis of another type has been observed by Powell[15]: Muscular weakness and atrophy simulated progressive muscular dystrophy. Powell made the interesting observation that in six of the seven cases with autopsy in which sarcoidosis of skeletal muscles has been reported, myocardial sarcoidosis has been found.

Sarcoidosis of the Gastrointestinal Tract

Anorexia and weight loss are common and often severe symptoms of sarcoidosis, but, with the exception of hepatic involvement, gastrointestinal sarcoidosis is extraordinarily rare.[16] Sarcoid infiltration of the stomach has been reported in a half-dozen instances, either as part of generalized sarcoidosis or in an isolated form. Sarcoidosis was responsible for a stenosing lesion of the sigmoid in one of our cases.

Sarcoidosis may rarely involve the small intestine, producing a clinical picture simulating regional enteritis, but it is generally conceded now that regional enteritis itself is an unrelated entity.

Hepatic and Splenic Sarcoidosis

Hepatosplenomegaly is detectable clinically in approximately 15% of cases of sarcoidosis, but microscopic involvement is much commoner. Epithelioid tubercles occur in the liver in 80% of patients with this disease, so that aspiration biopsy of the liver provides a useful method of demonstrating sarcoid lesions. However, as Klatskin and Yesner[17] have pointed out, many other diseases produce epithelioid granulomas in the liver, notably tuberculosis, brucellosis, histoplasmosis, infectious mononucleosis, and viral hepatitis. Liver biopsy is consequently a ready means of finding histologic evidence of sarcoidosis, but a poor means of differentiating sarcoidosis from other granulomatous diseases.

Symptoms referable to the hepatic involvement are infrequent, although the anorexia and weight loss which are so characteristic of sarcoidosis may be due to hepatic dysfunction.

Liver function tests are frequently abnormal in patients with sarcoidosis. Abnormal flocculation tests, however, are often the result of the elevated γ-globulin which characterizes sarcoidosis. Sulfobromophthalein (Bromsulphalein) retention occurred in almost half the patients studied by Shay and his associates.[18]

Splenic infiltration by sarcoidosis may result in marked enlargement of this organ. Instances of hypersplenism are encountered, and it should be noted that leukopenia is a common and marked feature of this disease.

Osseous Sarcoidosis

Roentgenologists have long been familiar with the occurrence of lesions in the bones of the hands and feet of patients with this disease, but estimates as to their frequency and the clinical value of their demonstration have varied widely. The frequency observed in one American study was 20%,[19] whereas a Scandinavian study demonstrated osseous lesions in only 6%.[20] We recently studied 81 patients with sarcoidosis and found characteristic osseous changes in 17.2%.[21] The changes indicative of sarcoidosis fell in three categories: (1) single or multiple rounded radiolucencies in the epiphyses, often referred to as "punched-out" lesions; (2) diffuse thinning of the cortex and widening of the medulla with a reticular pattern of the trabeculae, producing a honeycombed configuration, and (3) coalescing lesions, producing destruction of the bone. The bones of the hands alone were involved in nine patients, and in three the bones of the feet alone were affected; two patients showed lesions in both hands and feet.

The roentgenographic demonstration of osseous lesions is important because their presence provides useful evidence to support the diagnosis of sarcoidosis. Osseous lesions of this type are rare in tuberculosis, histoplasmosis, and berylliosis, the diseases which commonly produce histologic and clinical changes similar to those of sarcoidosis. Hence, the demonstration of the lesions in the hands or feet is valuable corroborative evidence for the diagnosis of sarcoidosis. Roentgenographic study of the bones of the hands and feet should be a part of the examination of all patients in whom sarcoidosis is suspected.

Cutaneous Sarcoidosis

The cutaneous lesions appeared to be especially common and unusually varied in character in the Negro.[22] The eruptions in general assume at least three different forms: (1) small, discrete, slightly elevated nodules; (2) large conglomerate masses, protruding a little and involving the subcutaneous tissue; (3) large, flat plaques covering considerable areas of the skin over the trunk and extremities. The small nodules, which are by far the most frequently seen, are usually to be found over the face, about the eyelids and nares, or over the ears and around the shoulders and the upper extremities. They vary from a few millimeters to a centimeter or so in diameter, and are slightly elevated, yellowish, or purplish in color. The surface is dry and apt to be a little scaly. There is never pustulation or ulceration. These small nodules are occasionally numerous, but not infrequently they are so sparse that a careful search of the entire body is necessary before they can be found. The large, more or less lobulated granulomata, which, like the small nodules, are firm and dry, frequently have a purplish tint. They occur on the nose, where they are very conspicuous, or about the joints of the hands and feet, where they are likely to be pale. The third variety is quite different from either of these, for it is a large, flat, very finely granular or scaly lesion which covers in patches large areas of the skin, principally over the extremities or trunk.

Endocrine System

Sarcoidosis exhibits a striking predilection for one endocrine gland, the pituitary. Sarcoid involvement is not uncommonly

responsible for diabetes insipidus or panhypopituitarism.

On the other hand, sarcoid infiltration of the thyroid, pancreas, ovaries, testes, and adrenals rarely, if ever, occurs. Several cases of sarcoidosis of the adrenals were reported by Ricker and Clark,[23] but, on restudy, these proved to be instances of histoplasmosis which had erroneously been considered to be sarcoidosis.[24,25]

Hypercalcemia and Nephrolithiasis

An uncommon, but most intriguing, manifestation of sarcoidosis is hypercalcemia. Occurring in approximately 15% of patients with this disease, its recognition is of prime clinical importance. If uncorrected, prolonged hypercalcemia and hypercalciuria will result in nephrolithiasis and eventual renal insufficiency. The hypercalcemia appears to be the result of excessive absorption from the gastrointestinal tract, and the abnormal calcium metabolism is promptly reversed by administration of corticosteroids.[26] It is important that this syndrome be recognized so that steroid therapy may be instituted and maintained in dosage adequate to control the hypercalcemia.

Diagnosis

A clear-cut distinction should be made between the *sarcoid reaction*, which is a histologic diagnosis, and the disease *sarcoidosis*, which is a clinical diagnosis, not to be made by the pathologist. The diagnosis of sarcoidosis requires, in addition to demonstration of consistent histologic changes, clinical, laboratory, and radiologic evidence, as well as careful exclusion of the diseases which simulate sarcoidosis. Most patients with this disease exhibit a characteristic clinical picture, and in these instances the diagnosis can be made with a high degree of accuracy.

Sarcoidosis is a systemic disease, and in order to establish its presence, systemic involvement must be demonstrated. This may be done by multiple biopsies, but ordinarily roentgenologic or clinical evidence of involvement in organs other than the site of biopsy suffices. Thus, an isolated skin lesion which on biopsy shows epithelioid tubercles may represent a foreign-body reaction; but if, in addition, there is pathologic evidence of similar lesions in a lymph node or the liver or if there is roentgenologic evidence of mediastinal adenopathy or skeletal changes in hands and feet, or if characteristic ocular changes are observed, the diagnosis of sarcoidosis may be made with assurance.

When clinical manifestations are atypical, on the other hand, the diagnosis of sarcoidosis should not be made without exhaustive investigation to exclude tuberculosis and the numerous other causes of epithelioid granulomas. This will require such special studies as fungal skin tests, serologic tests for fungal infection, and culture of biopsy specimens.

Histologic study is only a part of the evidence on which the diagnosis of sarcoidosis is based, but it is an important part. The difficulties and errors in diagnosis which may occur when pathologic studies have been carried out are multiplied when one attempts to make the diagnosis without such studies. Moreover, the excised tissue provides an opportunity for bacteriologic, mycologic, and chemical examinations. Careful study of sections stained with Ziehl-Neelsen and Hotchkiss-McManus techniques may establish the presence of tuberculosis or fungal disease in tissues that might otherwise be regarded as characteristic of sarcoidosis. Spectrographic analysis of lung biopsy specimens is indicated in patients whose occupational or residential history suggests exposure to beryllium.

Biopsy Procedures.—When cutaneous lesions are present or peripheral lymphadenopathy is detected, tissue for biopsy is readily available. The smallest of palpable lymph nodes is adequate for this purpose: Lymph nodes of a size that would be insignificant in other diseases will frequently demonstrate a sarcoid reaction. In half of our patients, however lymph nodes were

not palpable, or lymph nodes biopsies failed to reveal characteristic epithelioid tubercles. Under these circumstances, several means may be utilized to produce tissue for study. Needle aspiration biopsy of the liver is a useful method, affording positive results in a high proportion of patients with sarcoidosis. Although the liver is an organ in which granulomas are readily demonstrated, it should be emphasized that liver biopsy is not a good means of differentiating granulomas of various etiology.

Scalenus fat pad biopsy will frequently yield small nodes that show a sarcoid structure. This appears to us a useful method in the patient with mediastinal lymph node enlargement but no pulmonary infiltration.

When disseminated pulmonary lesions are roentgenologically demonstrable, the most satisfactory method in our experience is the closed intercostal pulmonary biopsy, of the type described by Klassen and his associates.[27] The procedure can be carried out under local or thiopental (Pentothal) anesthesia, and produces no more discomfort than excision of an axillary lymph node or a scalene fat pad biopsy. Our increasing use of pulmonary biopsy is indicated in Table 9. Data indicating the relative value of various biopsy procedures are shown in Table 10.

The laboratory tests which are useful in supporting a diagnosis of sarcoidosis include a negative tuberculin test, increased γ-globulin, leukopenia, and hypercalcemia. These are characteristic features of sarcoidosis whose presence lends valuable support to the diagnosis of sarcoidosis; their absence does not contravene the diagnosis. Although many investigators[28] have found the Kveim reaction useful in diagnosis, most observers consider the test unreliable because of the impossibility of maintaining adequate supplies of standardized test materials.[29] Additional objections to this test include the difficulties in histologic interpretation and the ever-present danger that the test material has lost specificity.[30] The controversy over the diagnostic value of this test is of little practical concern. No antigen is available for the test unless one prepares and standardizes one's own.

The differentiation of sarcoidosis, tuberculosis, and fungal infection is a constant concern. It is to be emphasized that sarcoidosis may be simulated by these other infections, or these diseases may develop in persons who have true sarcoidosis. Careful bacteriologic, mycologic, and serologic study of atypical cases of sarcoidosis will minimize the likelihood of errors in diagnosis. The declining prevalence of tuberculous infection has in recent years reduced the hazard of tuberculosis as a sequel to sarcoidosis, but prolonged observation indicates that patients with sarcoidosis are at greater risk than the general population of contracting tuberculosis. This greater susceptibility is similar to that noted among patients with silicosis, and is presumably due to the lowered resistance to infection of damaged lungs.

TABLE 9.—*Source of Initial Positive Biopsy Specimens in 160 Patients with Sarcoidosis*

	1938-1947	1948-1951	1952-1956
Peripheral lymph node	17	35	37
Skin	9	8	5
Lung	0	2	17
Liver	0	9	3
Scalene	0	0	3
Other	1	8	6
Total	27	62	71

TABLE 10.—*Likelihood of Demonstrating Sarcoid Tubercles in Various Biopsy Sites*
Analysis of 230 Biopsies in 160 Patients with Sarcoidosis

	No. of Biopsies	Percentage Positive
Lymph nodes		
Cervical	57	89.1
Axillary	38	81.7
Inguinal	18	88.9
Epitrochlear	9	100.0
Scalene	5	60.0
Liver	24	91.7
Lung	20	100.0
Skin	27	100.0
Muscle	6	50.0
Marrow	6	16.7
Parotid	3	100.0

Prognosis

There have been remarkable variations in reported observations concerning the course of sarcoidosis. One of the earlier American studies by King,[31] of Boston, indicated that the disease was almost invariably benign; of 37 patients none died, only 3 worsened, and 26 improved. Reisner[32] and Riley,[4] in New York, had less favorable experiences; 7 of Reisner's 28 patients died, in 6 instances with tuberculosis. Tuberculosis developed in 13 of Riley's 52 patients, and only 17 showed any improvement. Carr and Gage, on the other hand, observing 194 patients whose disease had been diagnosed at the Mayo Clinic, found only 3 deaths from sarcoidosis and 1 from tuberculosis. The survival rate of patients with sarcoidosis 10 years after diagnosis was 88% of the normal.[5]

Still a different picture is presented by Nitter, who studied 90 cases in Norway; 16 patients died, in only 1 instance of tuberculosis.[20] Fifteen other patients were suffering respiratory embarrassment from advanced pulmonary fibrosis.

Our own observations on 160 patients demonstrate a mortality rate of 8.1%.[33] Two deaths were due to tuberculosis; the other eleven, to progressive sarcoidosis. Complete clearing of symptoms and radiologic changes was observed in 34.2% of the group, and an additional 27.4% were classified as improved.

No large series of cases has been followed for an adequate length of time. It is evident that there is marked variation in the outcome of this disease. Whether the prognosis is influenced by such factors as economic status and race has not been determined.

Tuberculosis has proved to be a complication in 6 of our 160 cases. It is our brief that if painstaking care is used to exclude at the outset cases of atypical tuberculosis which simulate sarcoidosis, under present circumstances tuberculosis should rather infrequently supervene in cases of sarcoidosis.

Treatment

A variety of agents, including the commonly used antibiotics, mechlorethamine (nitrogen mustard), radiation, calciferol, and urethan, have been tried in sarcoidosis, without consistent benefit. It is of special interest that isoniazid exerts no demonstrable influence on the course of sarcoidosis, a fact which argues strongly against a tuberculous etiology of this disease.[34]

The only agents which have proved of value are the corticosteroids: cortisone and its derivatives and corticotropin. The effect on some manifestations of sarcoidosis is dramatic; patients acutely ill with uveoparotid fever may show disappearance of fever, parotid swelling, and ocular symptoms in 24 hours. The effect on mediastinal adenopathy, on the other hand, may be minimal.

Symptomatic improvement is obtained in most cases. Marked improvement was described by 61% of our patients with symptoms of less than six months' duration, while a similar degree of improvement occurred in only 29% of patients with symptoms of longer duration.[35] In a few patients whose diffuse pulmonary lesions showed no response to cortisone, marked clearing later occurred spontaneously. It should not be assumed that sarcoid lesions unaffected by cortisone are irreversible.

No controlled studies over long intervals have been carried out to determine to what degree the eventual course of the disease is influenced by cortisone. A favorable outcome is achieved much more rapidly in some patients, however, and physiologists have urged the use of steroids in all cases of sarcoidosis in the hope of preventing disabling fibrosis in some. Unfortunately, sarcoidosis is not infrequently simulated by or superinfected with tuberculosis and fungal infections, and these hazards are a constant concern when steroids are used in the treatment of sarcoidosis. The danger is small in our experience, but it is evident from the experience of others that this danger cannot be disregarded. Accordingly, it appears judicious to restrict the use of

cortisone to selected cases of sarcoidosis: to those with persistent respiratory symptoms, and to those with ocular involvement, myocardial infiltration, uveoparotid fever, erythema nodosum, blood dyscrasias, or central nervous system involvement. A clear indication for prolonged corticosteroid therapy is hypercalcemia, which will, if uncorrected, result in serious renal damage.

Fortunately, the indications for use of cortisone are strongest in those forms of sarcoidosis in which, as noted above, there is least danger of confusion with tuberculosis. Corticosteroids are most effective in acute uveitis, parotitis, myocardial involvement, and hypercalcemia. These manifestations are rarely due to tuberculosis, and patients who have weakly positive or negative tuberculin tests, hyperglobulinemia, biopsy specimens demonstrating noncaseating tubercles, and involvement of eyes, parotid glands, skin, heart, liver, or spleen may be given steroids with confidence. On the other hand, careful bacteriologic and mycologic study is advisable before administering these agents to patients with strongly positive tuberculin reactions, evidence of oral and laryngeal ulcers, serosal effusions, adrenal insufficiency, or other manifestations rare in sarcoidosis.

Cortisone and its derivatives appear to be as effective as corticotropin, and are more conveniently administered. An initial daily dose for the adult of average weight is 40 mg. of prednisone or prednisolone for 10 days. The dose is gradually reduced to the lowest level which maintains the desired effect. The total duration of treatment is one to two months in most instances. Occasionally, patients with advanced respiratory insufficiency obtain such symptomatic relief from steroid therapy that they are unable to tolerate its discontinuance.

One notes occasionally the practice of adding antituberculous chemotherapy whenever corticosteroids are employed in treatment of sarcoidosis. It is difficult to justify this procedure unless the antimicrobial drugs are given for 18 to 24 months. Surely no protection against tuberculosis will be obtained by use of chemotherapy for only the few weeks or months that corticosteroids are administered. Since only one of the many patients with sarcoidosis to whom we have administered corticosteroids subsequently developed tuberculosis, we believe that the routine use of prolonged antituberculous chemotherapy is not warranted.

Instances have also been encountered in which, through fear of tuberculosis, corticosteroid therapy has been withheld from patients seriously ill with sarcoidosis. We are increasingly impressed with the therapeutic value of these agents, and, although their use is inadvisable in the asymptomatic patient, the patient who is ill with sarcoidosis should not be denied the benefit of this medication.

Summary

1. Sarcoidosis has become, in Scandinavia and in the eastern United States, a common disease.

2. Observations on 160 patients with diagnoses supported by biopsy demonstrate the wide range of clinical manifestations of this disease.

3. Corticosteroid therapy is indicated in many cases of sarcoidosis, and can safely be given to patients whose diagnosis is supported by careful clinical and laboratory study.

Dr. George Babcock, Associate Medical Director, Schering Corporation, gave generous supplies of prednisolone (Meticortelone).

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Hodgkin's Disease and Pregnancy

Case Reports and a Discussion of the Treatment of Hodgkin's Disease and Leukemia During Pregnancy

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Introduction

Hodgkin's disease complicated by pregnancy constitutes a situation in which the mother is burdened by two proliferating systems, the disease and the fetus. One demands elimination or control; the other, preservation. During the past year we were confronted by this problem six times, and on several occasions treatment was urgently indicated. We reviewed the subject to learn the experience of others. Numerous papers were available on the influence of pregnancy on Hodgkin's disease and the question of therapeutic abortion, but little information was found relevant to the problem of control of the disease and preservation of the fetus when therapy is demanded. Irradiation has been employed frequently, but the chemotherapeutic agents have not been used sufficiently to permit adequate evaluation of their effect on pregnancy. It is advisable to use the antimetabolites and alkylating agents and, if so, when during pregnancy are they least harmful to the fetus? The problem is not a rare one among women with Hodgkin's disease, and although there is as yet no definitive answer to the question of therapy, we have summarized our recent experience against a background of the published reports.

Walter Reed Army Hospital Series

During the period 1942-1957, fifty-six women between the ages of 15 and 50 were registered at Walter Reed Army Hospital with the diagnosis of Hodgkin's disease. Of this number, 18 patients (33%) bore children in the course of their disease, with a total of 21 pregnancies (Table 1). Five of these cases were noted in an earlier report by Riva et al.[1] In all cases the diagnosis of Hodgkin's disease was established by biopsy and the sections were reviewed at the Armed Forces Institute of Pathology. The majority were reported simply as Hodgkin's disease without subclassification. Since the available clinical data are incomplete, dates of x-ray treatment have been given to provide some supplemental information on the patients' courses. Complete irradiation data, where available, are given only in the cases treated during pregnancy. The dosage of x-ray irradiation is that which is generally employed at Walter Reed for the treatment of Hodgkin's disease.[2] Chemotherapeutic agents were used when the disease was disseminated or systemic symptoms were severe. However, treatment was avoided during pregnancy unless the indication was urgent. Case reports illustrating this point are appended.

In most of the patients, Hodgkin's disease was present at the time of conception, but in six of them it was discovered during the pregnancy or within three weeks after delivery (Table 1, Cases 4, 7, 8, 9, 15, and 18). In no case was it possible to say that the course of the disease had been altered one way or another by the coincidence of pregnancy. In one case there was a spontaneous abortion at about three months (Case 6). In no case was therapeutic abortion performed. The 20 children born of these pregnancies were sound and healthy; follow-up has revealed no instance of neoplastic disease. In the cases where treatment was necessary, the disease showed no un-

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TABLE 1.—*Walter Reed Army Hospital Cases of Hodgkin's Diseases Complicated by Pregnancy from September, 1943, to 1957* *

Case No. (Age at Onset)	Onset of Symptoms (Biopsy)	Findings on Recorded Admissions to WRAH †	Treatment †	Pregnancy	Infant's Condition at Birth	Maternal Follow-Up, Mo.	Maternal Follow-Up Postpartum, Mo.	Infant Follow-Up, Mo.
1 (19)	Sept. 1943 (Oct. 1943)	Sept. 1943: chest pain; Feb. 1945: fever, fatigue, wt. loss, med. mass	X-ray: Oct. 1943, med.; March 1944, med. & s'cl.; April 1945, epigastrium	June 1944–April 1945	Normal; term; C-sect.	21 (died)	2	—
2 (20)	Jan. 1948 (May 1949)	Jan. 1948: anemia, wt. loss following spontaneous abortion; March 1949: med. mass, wt. loss	X-ray: June 1949, med.	Sept. 1949–June 1950	Normal; term	40 (lost)	25	25
3 (28)	Dec. 1951 (April 1953)	Dec. 1951: cv. node.; April 1953: cv. & med. nodes, superior vena cava syndrome	HN2 April 1953; x-ray: June-July 1953, lt. cv., med.; Jan. 1954, July 1955, May & July 1956, cv. & med.	Oct. 1956–July 1957	Normal; term	68 (alive)	3	3
4 (35)	Sept. 1950	Sept. 1950: rt cv. & ax. nodes, hemoptysis 1 wk. antepartum	X-ray: Sept., Nov. 1950, Feb.-March 1952, March 1953, cv.; April 1956 inguinal nodes	Dec. 1949–Sept. 1950	Normal; term	69 (lost)	69	69
5 (24)	Oct. 1954 (Sept. 1955)	Oct. 1954: fatigue, dyspnea; April 1957: dysphagia	HN2; x-ray: Nov. 1955, med.; March 1956, ax. & med.; Oct. 1956, cv. & med.	Dec. 1956–Aug. 1957	Normal; term	24 (alive)	1	1
6 (20)	April 1953 (April 1953)	April 1953: lt. cv. node.; April 1954: fever, cv. & abd. nodes	X-ray: April 1953, cv. & ax.; HN2: April 1954; x-ray: May 1954, cv. abd.	Feb.-April 1954	Spont. ab.	28 (died)	15	
7 (22)	March 1956 (July 1956)	March 1956: cough, med. & cv. masses, progressive	None during pregnancy, at least	Oct. 1955–July 1956	Normal; term	6 (lost)	9	6 wk.
8 (27)	July 1953 (Nov. 1953)	July 1953: med., cv., ax. nodes; had delivered in June 1953; Nov. 1953: lt. cv. & ax. nodes, med. mass	X-ray: Nov.-Dec. 1953, 2,500 T lt. ax. 2,500 T lt. cv. 3,000 T med. (1,000 kv., 3.6 Pb)	Oct. 1953–July 1954	Normal; term	31 (died)	19	
9 (25)	April 1956 (April 1956)	April 1956: cv. nodes	X-ray: May-June 1956, 2,444 T med. (1,000 kv., 3.6 Pb) 2,480 T rt. cv. 2,480 T lt. cv. (200 kv., 1.0 Cu) July 1956, 1,600 S lt cv (200 kv. 1.0 Cu)	Jan.-Oct. 1956	Normal; term	16 (alive)	11	11
10 (20)	Jan. 1949 (July 1949)	Jan. 1949: lt. cv. nodes, wt. loss; July 1949: lt. cv. & med. nodes	X-ray: July-Aug. 1949, 2,480 T med (1,000 kv., 3.6 Pb) Aug. 1949, 2,500 S s'cl. (200 kv., 1.0 Cu) April-May, 1950 2,200 S rt. s'cl. 2,400 S lt. s'cl. (200 kv., 1.0 Cu) 2 more courses in 1955	Aug. 1949–May 1950	Normal; term	85 (lost)	68	64
11 (25)	May 1949 (Jan. 1950)	May 1949: cv. nodes; Jan. 1950: cv. ax., & med. nodes; fatigue	X-ray: July 1950, 2,600 S submental Aug. 1950, 2,100 S each ax. Nov. 1950, 3,000 S lt. cv. (all 200 kv. 1.0 Cu)	July 1950–April 1951	Normal; term	68 (died)	45	1

12	1949	1949: ev. & med. nodes	X-ray: 1949	Dec. 1948–Sept. 1949	Normal; term	24 (lost)			
13 (28)	June 1948	June 1948: ev. ax. nodes; osteolytic lesion rt. acromion; Feb. 1951: same, post auricular nodes; Dec. 1952: same, plus wt. loss, anemia, dyspnea, hemoptysis	X-ray: June 1948, rt. shoulder, ev. ax. April, June, Aug., Dec. 1951, April 1952 ev. & med. Nov. 1952, 3,600 S rt. shoulder (200 kv., 1.0 Cu) Jan. 1954, rt. shoulder, retroperitoneal nodes	Sept. 1950–May 1951 July 1952–March 1953	Normal; term Normal; term	78 (died)	43		
14 (22)	Aug. 1947 (Dec. 1950)	Dec. 1950: ev., ax., breast & abd. masses; weakness, nausea	X-ray: Aug. 1947, Oct. 1948, ev. April 1949, Jan. 1950, lt. ax., ev.	1949 Jan.-Oct., 1951	No data Normal term	58 (died)	322 8		
15 (22)	May 1947 (June 1947)	May 1947: ev. nodes; May 1948: ev. nodes; March 1952: schizophrenia	X-ray: July 1947, 1,300 A lt. s'cl. 1,800 T med.	Dec. 1946–Sept. 1947 May 1948–Feb. 1949	Normal; term Normal; term	38 (lost)	54 38	54	38

* Cases 16, 17, and 18 are detailed in the addendum; see also Table 3.
† Cv. indicates neck; s'cl., supraclavicular area; ax., axilla; med., mediastinum; abd., abdomen; T., tumor dose; S., skin dose; A., dose in air. X-ray doses are in roentgens.

usual sensitivity or resistance to the therapeutic agents employed and the patients tolerated the treatment well.

Comment

Incidence of Pregnancy in Hodgkin's Disease.—The rarity of Hodgkin's disease complicated by pregnancy has been mentioned by many authors. While the absolute incidence of this combination may be low, it is to be expected among women with the disease. The incidence of pregnancy in our series of 65 women with Hodgkin's disease in the age range 15-50 was 33%. During our review of the medical literature bearing on this subject, we made a compilation of 603 females with Hodgkin's disease [3-15] and found that 110 pregnancies had occurred, for an incidence of 18%. Unmarried women and women not in the child-bearing age were excluded from the compilation where this information was available.

Influence of Pregnancy in Hodgkin's Disease.—Myles,[16] in a review of the world literature, has pointed out that pregnancy has no apparent effect on the course of Hodgkin's disease and, conversely, that Hodgkin's disease has little effect on pregnancy.* However, several authors believe that onset of Hodgkin's disease during pregnancy or the puerperium carries a poor prognosis.[4,12,42] Southam, Diamond, and Craver [18] recently reported that the mean survival time in patients in whom onset of Hodgkin's disease occurred during pregnancy was significantly shorter (46 months) than in patients in whom onset occurred prior to conception (91 months). However, the marked difference between the two groups may be explained by the fact that there is necessarily a selection of favorable cases in the group who conceived after the onset of Hodgkin's disease, since patients with severe or fulminating disease either do not survive or do not conceive. It must be stressed that onset of Hodgkin's disease during pregnancy is not incompatible with

* It has also recently been shown that pregnancy probably has no effect on the course of chronic leukemia.[17]

TABLE 2.—*Cases of Hodgkin's Disease Treated with Roentgen Irradiation During Pregnancy*

Case No.	Author	Treatment & Its Relationship to Pregnancy in Time	Outcome of Pregnancy	Infant Follow-Up, Yr.
1	McSwain & Haber	1st mo.: 1900 r to axilla & 1900 r to neck; treatment may have preceded pregnancy in part	Normal	2
2	Adair	3d mo.: unspecified dose & site	Normal	3
3	Olmsted	3d mo.: 22 r to upper half of body	Normal	6
4	Kasdon	In 1 st trimester, 2500 r; in 2d, 4500 r to chest; in 3d, 5000 r to mediastinum	Term: infant died in 4 days, with atelectasis	
5	Kushner	In 1 st trimester, 1200 r; treatment may have preceded pregnancy in part	Normal	2½
6	Stewart & Monto	2d mo.: "Initial course of deep x-ray"	Normal	11
7	Paviot et al.	In 1st trimester, unspecified dose to mediastinum; mother died in 6th mo.	Fetus apparently "normal"	
8	McDonald	2d mo.: neck & thorax irradiated	Hysterotomy at 21 wk.; mother very ill, died 6 wk. later	
9	Erf	1st mo.: 3000 r, presumably to neck	Hysterotomy at 5 mo.	
10	Hartweg & Braun	Probably in 1 st trimester, x-ray to cervical nodes	Normal	
20	Tenenblatt & Horton	5th mo.: 900 r to neck & mediastinum with fetus shielded	Normal	1
21	Brougher	5th mo.: 864 r to neck & chest	Normal	
22	Harris, (W. H.)	4th mo.: 900 r to mediastinum, anterior	Infant died in 4 days, with acute yellow atrophy, pneumonia, blood pleural effusion, pulmonary edema	
23	Portmann & Mulvey	5th mo.: "4 r treatments in nature of spray"	Presumably normal; birth date cited	
24	Hartvigsen	5th or 6th mo.: x-ray to neck	Normal	
25	Bichel	5th (?) mo.: 305 r spray, with uterus shielded	Mother died in 7th mo.	
26	Nagel	In last 2 trimesters, 1800 r "deep dose" to mediastinum	Premature at 7 mo.	2 mo.
27	Mertens	8th mo.: intensive x-tay to neck & mediastinum	Normal	
28	Dyes	7th mo.: 1440 r to cervical & axillary nodes	Presumed normal	
29	Summers and Reid	In last trimester, "1 dose of 6 proposed"	Normal	½
30	Bastenie & Snoeck	In last trimester, 6400 r to neck & mediastinum, at least	Normal	17

long survival. Among the patients described by Southam et al. were women who had survived up to 150 months after diagnosis; three of our own patients were still living when last heard from, at 57, 58, and 69 months. Whether Hodgkin's arising in pregnancy truly carries a less favorable prognosis is a question which is currently under study.[18]

Treatment During Pregnancy.—A. Irradiation: The harmful effects of x-irradiation have been appreciated for many years.[19,20] Irradiation tends to cause fetal death early in pregnancy and teratogenesis later; sensitivity to radiation decreases as the fetus grows older.[21,22]

In the literature were found 48 cases of Hodgkin's disease treated with roentgen irradiation during pregnancy without the use of cytotoxic drugs.[10-13,23-44] These cases are listed in Table 2. The data in Table 2 indicate that conventional treatment of maternal lesions distant from the uterus has apparently not harmed the products of conception, regardless of fetal age at time of x-ray treatment. However, these children who have received scatter irradiation in utero have been exposed to the potential risk of delayed leukemogenesis and possibly to an increased risk of other malignancies.

In the 34 cases in which data were available (Table 2), two fetuses died as a result of maternal death due to Hodgkin's disease, four pregnancies were artificially interrupted, three infants died during the first month of life of causes by no means certainly related to the irradiation, and one child died at 10 weeks of life. Twenty-four children were apparently normal throughout follow-ups of varying length. Our several additional cases in Tables 1 and 2 also fail to show any apparent deleterious effect of

TABLE 3.—*Cases of Hodgkin's Disease and Leukemia Treated with Cytotoxic Agents During Pregnancy*

Author	Case No.	Age	Diagnosis	Onset Prior to Pregnancy, Mo.	Treatment	Infant's Condition at Birth	Infant Follow-Up, Mo.
Deuschle & Wiggins	1	26	HD	17	1 mo. before conception, x-ray to abdomen; in 3d mo., 2 one-wk. courses of 18.2 mg. colchicine; 4th mo., 0.6 mg/kg. HN2; next 3 mo. cervical & axillary x-ray	Normal	19
Deuschle & Wiggins	2	26	HD	5	In 4th mo. 0.4 mg/kg. HN2; 5th mo., 0.4 mg/kg. HN2; thereafter, unspecified amount of corticotropin (ACTH)	Normal (premature)	10
Boland	3		HD		Before pregnancy, 4 courses of 0.4 mg/kg. HN2; in 3d mo., another course (same dose)	Terminated at 5 mo. 1½ lb. fetus; lived 2 days	
Zoet	4	22	HD	108	At about time of conception, 0.1 mg/kg. HN2; in 2d trimester, possibly partly in 1st, x-ray 2,505 r to left arm, shoulder, axilla, & upper chest; 7th mo., HN2, no dose cited	Normal	8
Wright et al.	5	25	HD	Following delivery March 1951	From Oct. 1951, 4 courses triethylene melamine 15 mg. in 85 days; 21 days later put on maintenance (dose 1 mg. daily, probably) for 50 days, then aborted spontaneously; Later back on maintenance with 2d abortion 4 mo. after 1st		
Cariati	6	28	Acute hemocytoblastic leukemia	1-2	Patient received "Antifolica" in unspecified amount in 1st and/or 2d mo. of pregnancy	Spontaneous abortion at 2 mo.	
Harris, (L. J.)	7	27	ALL	2	In 1st trimester 13 mg. aminopterin in 9 days	Spontaneous abortion at 3½ mo.	
Bierman et al.	8	27	ALL	1½	In last trimester 70 mg. triethylene melamine in 2½ mo.	Normal	
Merskey & Rigal	9	25	ALL	2	Conceived while on mercaptopurine, 2.5 mg/kg.	Premature by 2½ mo.; lived 48 hr.	
Schumacher	10	23	AML	In 2d mo. of pregnancy	Cortisone, 100 mg. per day from 4th mo. to delivery; mercaptopurine 100 mg. per day for 7 wk. in 6th and 7th mo. (total 5.2 gm.)	Normal	
Rothberg et al.	11	35	AML	In 4th mo. of preg.	In 5th month; prednisone 60 mg/day ×8; mercaptopurine 175 mg/day×3	Premature (995 gm); lived 2 hrs	
Rothberg et al.	12	33	AML	In 4th mo. of preg.	Mercaptopurine 25-200 mg/day throughout last 4½ mos of pregnancy	Normal	4
Gillim	13	40	CML	9	Conceived while on urethan during 12-mo. course, which was continued into 4th mo. of pregnancy	Normal	16
Imber & Meharg	14	22	CML	In 3d mo. of pregnancy	From 4th mo. to term, urethan, 0.3 gm. daily	Normal	9
Creskoff et al.	15	30	CML	12	Conceived while on urethan, 4 gm. daily, continued into 1st trimester	Well in 7th mo. of pregnancy	
Erf	16	23	CML		P^{32}, 41 mc. total dose, in part given at some time during late pregnancy	Normal	
Erf	17	38	CML		P^{32}, 60 mc. total dose, in part given at some time during late pregnancy	Normal	
Newsom et al.	18	40	CML		P^{32} in 8th wk. of unsuspected pregnancy	Premature at 35 wk.; stillborn, macerated	
Lessmann & Sokal	19	38	CML	12	Demecolcin 1 to 8 mg/day throughout pregnancy; conceived while on therapy	Normal	2
Sherman & Locke	20	31	CML	6	Myleran 4 to 6 mg/day in 2nd & 8th mo. of pregnancy	Normal	12
Izumi	21	31	CML	8	Myleran 1 to 4 mg/day throughout pregnancy; conceived while on therapy	Normal but small (1985 gm) (Japanese)	1

x-ray delivered to maternal lesions distant from the uterus.†

B. Cytotoxic Drugs: Reports of only seven patients with Hodgkin's disease treated with alkylating agents during pregnancy were found in the literature; there were an additional 15 patients with leukemia in pregnancy treated with various cytotoxic drugs. These, with our four cases, have been compiled in Table 3.[29,45-56] Since little clinical material has been reported, it may be of value to review the data from studies in experimental mammals. The drugs used include the alkylating agents HN2 (methylbis[β-chloroethyl]amine, chlorambucil(*p*-[di-2-chloroethyl]aminophenyl butyric acid), and triethylene melamine (TEM); the antimetabolites, aminopterin (4-aminopteroyl glutamic acid), mercaptopurine (6-mercaptopurine), demecolcine (Colcemid[desacetylmethylcolchicine]), and urethan (ethyl carbamate).

1. Alkylating agents. The effects of the alkylating agents on pregnancy vary with the dose and the time of their administration.[59-61] For example, Murphy, Dagg, and Karnofsky[62] have shown that pregnant rats given 0.3-0.5 mg. of NH2 per kilogram intraperitoneally on the seventh day of their 22-day gestation will completely resorb fetal and placental structures. The same treatment given later in pregnancy produces only occasional resorption of implantation sites but yields a high percentage of stunted fetuses with a variety of gross abnormalities, especially of the central nervous system and skeleton. The highest incidence of these malformations occurs when the drug is administered on the 12th day, and even at this time doubling or tripling the dose will cause fetal death and resorption of implantation sites. Similar relationships have been demonstrated for triethylenethiophosphoramide (thio-TEPA), busulfan (Myleran), triethylene melamine, and chlorambucil; in each case the fetal L. D_{50} is considerably less than the maternal L. D_{50}.[63] Murphy and Karnofsky[64] have emphasized that in contrast to the antimetabolites the teratogenic effects of alkylating agents and x-ray are readily demonstrable up to the 16th day of gestation in the rat. Since these agents are believed to act on performed nucleoprotein rather than as inhibitors of nucleoprotein synthesis, it is possible that they may be deleterious even relatively late in pregnancy. However, induction of teratogenesis late in the fetal development of the rat requires doses that approach the maternal L. D_{50}.

Only eight patients treated with alkylating agents have been reported, plus the three of this paper (Table 3). One patient conceived and aborted twice while on triethylene melamine; one patient's pregnancy was artificially terminated at five months, and two aborted spontaneously after HN2 early in unrecognized pregnancy (Croizat, Table 3). With the possible exception of the second case of Deuschle and Wiggins (Table 3), seven infants showed no evidence of harm. In one of our cases triethylene melamine was used in a small dose in the first trimester; Boland's case was treated with HN2 in the third month, and both of Deuschle and Wiggin's cases were treated with HN2 in the fourth month. Two cases are known to have received HN2 within the month preceding pregnancy without harm to the fetus (Zoet, Table 3, and Case 17, Table 1).

2. Antimetabolites. None of the antimetabolic drugs so far developed are useful in Hodgkin's disease. In the leukemias, where they are of great value, pregnancy presents problems in treatment that may dif-

†Although radiophosphorus is not used in the treatment of Hodgkin's disease, it is a useful agent in chronic leukemia. It presents an entirely different problem from that of x-irradiation, since it readily crosses the placenta and is incorporated rapidly into fetal tissues, which are extremely susceptible to radiation; shielding is of course impossible. In two cases cited by Erf (Table 3) an unspecified dose was given late in pregnancy with no untoward sequelae mentioned. In Newsom's case (Table 3) the fetus was inadvertently exposed at six to eight weeks and was subsequently stillborn as a macerated 3 lb. 12 oz. infant. While this clinical evidence is meager, on theoretic grounds we consider radiophosphorus contraindicated in pregnancy.

fer considerably from those of the pregnant patient with Hodgkin's disease. In acute leukemia and in chronic leukemia in blast crisis the disease is fulminating, and there may be no possibility of deferring prompt and vigorous treatment until a less critical period of pregnancy.

The antimetabolites as well as the alkylating agents have abortifacient and teratogenic properties. Thiersch and Phillips[65] found that the folic acid antagonist, aminopterin, administered to pregnant rats at about the time of placental implantation, in doses that produced only transient marrow depression in the mothers, would bring about a high incidence of fetal death and resorption. Histologic study showed the major site of drug action to be on the embryonic mesenchyme rather than on decidual or placental tissue. Comparable doses (0.2-0.5 mg. per kilogram, or 8-24 mg. total) of aminopterin,[66] given during the first or second month of pregnancy, produced therapeutic abortion in 10 of 12 human mothers; fetal abnormalities were noted in 3 cases in which the fetal age at the time of treatment was estimated to be 40, 49, and 54 days, respectively. The relation between the time of antimetabolic action and the end-result has been most clearly demonstrated by Nelson,[67] using a folic acid-deficient diet containing x-methyl-pteroylglutamic acid. When this diet was fed to rats during the 8th to 10th days of gestation, resorption occurred in 100%. The same regimen on the 9th to 11th days was followed by only 26% resorptions; but of the surviving progeny, 99% were abnormal; when the diet was given on the 10th to 12th days, there were no resorptions and 78% abnormal progeny. When the regimen was instituted at progressively later times (after the 12th day), fewer and fewer abnormalities were produced. The major period of organogenesis in the rat occurs from the 10th to the 12th days, which corresponds to the period of maximum susceptibility to the teratogenic effects of antimetabolites.

Purine analogs may be expected to have a similar influence on the course of pregnancy. Thiersch[68] found a high incidence of embryonic death and general stunting of surviving fetuses of pregnant rats treated with mercaptopurine. No gross malformations were observed in these experiments, but this may be attributed to the fact that the drug was not administered during the major period of organogenesis. However, Zunim and Borrone[69] subsequently noted hydrocephalus, microphthalmia, and anophthalmia in the progeny of rats given a relatively large dose of mercaptopurine from the fifth to the ninth day of gestation. Interestingly enough, one of our patients (Case 19, Table 3) conceived while on mercaptopurine, and Mersky and Rigal also reported such a case (Table 3). Neither pregnancy was successful; both infants were premature and died in the first 48 hours of life. However, both of these mothers had acute leukemia, in which the prognosis for fetal survival is notoriously poor in any case.

3. Other drugs. Other drugs are available for the treatment of Hodgkin's disease and leukemia during pregnancy. The use of urethan has been reported in three pregnant mothers with leukemia without apparent damage to the offspring. Steroids may be of benefit in lymphomas and acute leukemia and may allow remission long enough to ensure a viable infant; however, under some circumstances steroids also may be teratogenic,[70] and it has been suggested that steroids may accelerate the course of acute granulocytic leukemia.[71]

C. Therapeutic Abortion: The question of therapeutic abortion inevitably arises. Myles, in his review,[16] stated that exacerbation of Hodgkin's disease is no more frequent in pregnant than in nonpregnant women. He believes that interruption of pregnancy is justified only when the disease urgently requires treatment and is localized in the abdominal or inguinal regions and adequate radiotherapy is prevented by risk of injury to the fetus or where deep radio-

therapy has been administered to the abdomen during very early pregnancy. However, where treatment of lesions near the uterus is necessary, we believe that the alkylating agents are preferable to irradiation.

If cytotoxic drugs are used in the latter trimesters of pregnancy in their usual doses we would *not* recommend therapeutic abortion. In the first trimester it is probable that the use of small doses of alkylating agents is not an indication for abortion; on the other hand, if large doses of alkylating agents have inadvertently been administered, or if their use appears to be required by the clinical situation, then therapeutic abortion may be justified. Similarly, in a recent review of the subject of leukemia in pregnancy, it was concluded that therapeutic abortion was not ordinarily indicated.[17]

Conclusions

While it may be hazardous to draw conclusions from a very few clinical cases and from the extrapolation of animal data to man, the available evidence indicates that with each of the cytotoxic agents the greatest danger to normal fetal development exists during the period of major organogenesis, early in gestation. However, the danger to the fetus never disappears completely, even late in pregnancy. Nonetheless, HN2, triethylene melamine, and chlorambucil *have* been successfully used in human pregnancy without apparent harm to the fetus, and it would appear that the alkylating agents in conventional doses can probably be tolerated at least during the latter two trimesters. In the first trimester, even though the drugs have been given to a few patients without ill effect, the experimental evidence is so overwhelming that it would appear that such treatment should be avoided. Most pregnant women with Hodgkin's disease have localized disease for which radiation is the treatment of choice. In exceptional cases of generalized disease where therapy with the alkylating agents seems mandatory in early pregnancy, the dose must be kept to an absolute minimum. As for the antimetabolites, aminopterin and mercaptopurine, the available evidence suggests that they are contraindicated in the first trimester as far as the fetus is concerned. Colchicine and urethan have been used without harm, even in the first trimester, but the experience is too limited to permit conclusions. The question of dose in relation to the stage of gestation can only be answered with the accumulation of clinical experience. Since there is little relevant clinical information, it is important to report any cases which may help throw light on this matter.

A similar situation exists for x-radiation. Although there is abundant experimental evidence for the production of embryonic abnormalities by irradiation during organogenesis, clinical experience with radiation therapy in Hodgkin's disease has so far shown no instance of apparent harmful effect on the conceptus. Nevertheless, therapeutic radiation even of distant lesions should be avoided during the first trimester of pregnancy if at all possible. In the second and third trimesters, radiation therapy can probably be used for lesions distant from the uterus without risking production of congenital malformations. On the other hand, the possibility of an increase in the prevalence of leukemia or other malignancy in children surviving maternal irradiation is a risk that must be accepted in this group of patients. This risk also applies, for both radiation and mutagenic drugs, to the genetic changes that may become manifest in future generations. It is impossible to state at present whether a dose of radiation having a given effect on a cervical or axillary lymph node is more or less likely to affect the uterine contents than a comparable therapeutic dose of alkylating agent. It is certain, however, that whichever agent is employed, dosage during pregnancy should be restricted to the smallest amount needed to achieve the desired result.

In any case of Hodgkin's disease or leukemia with pregnancy in which treatment

is planned, the risk to both mother and fetus must obviously be considered. Each case requires separate evaluation of the total situation, including psychologic factors, and no hard and fast rules of therapy can be defined. In some cases risks must be assumed if viable infants are to be obtained at all.

Summary

Findings in 22 pregnancies in the course of Hodgkin's disease are presented. This represents an incidence of pregnancy in our series of 33%. In a group of 603 women with Hodgkin's disease, found in the literature, the incidence of pregnancy was 18%. The coincidence of pregnancy may be expected in any practice dealing with Hodgkin's disease.

There is no clear-cut evidence for a deleterious effect of pregnancy on the course of Hodgkin's disease. Therapeutic abortion is rarely indicated in patients with Hodgkin's disease.

Eighteen cases of Hodgkin's disease and leukemia treated with cytotoxic drugs during pregnancy are tabulated from the literature, with four of our own. Twelve normal infants resulted from these pregnancies. However, in most of these the therapy was not given at the critical period of fetal development.

Forty-eight cases of Hodgkin's disease treated with irradiation during pregnancy were found in the literature, and six cases of our own are added. Conventional radiotherapy of maternal lesions distant from the uterus produces no apparent harmful effect on the fetus. Nevertheless, radiation therapy should be restricted during pregnancy and avoided in the first trimester.

The hazards associated with the use of cytotoxic agents during pregnancy are discussed. Experimental evidence suggests that because of the abortifacient and teratogenic properties of alkylating agents and antimetabolites, their use in the first trimester of pregnancy should be avoided.

It is urged that cases treated with cytotoxic drugs during pregnancy be reported in detail.

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Addendum

CASE 16.—A 21-year-old white woman developed a cough in October, 1955, which led to the discovery of a large mediastinal mass in November. The diagnosis of Hodgkin's disease was established by thoracotomy biopsy. Between Dec. 22, 1955, and Jan. 25, 1956, the patient was given radiation therapy, with a tumor dose of 3030 r to the mediastinum. Her cough improved; her fever disappeared, and the mediastinal mass decreased in size. Her last menstrual period had begun on Dec. 1, 1955, and a Friedman test was negative Jan. 10, 1956. However, she returned to the hospital with painful left axillary nodes in April and spontaneously aborted April 11. After this she was treated with tumor doses of 2648 r to the left axilla and 2266 r to the right neck. In July, she was admitted to Walter Reed Army Hospital for the first time, with a bronchial ulceration attributed to her x-ray treatment. This cleared rapidly, and the patient remained well until January, 1957, when she presented with painful nodes in the left supraclavicular area and an associated Horner's syndrome. The pain became so intense that she required admission in late January, four and one-half months pregnant, with the findings described and recurrent mediastinal masses. Between Jan. 26 and Feb. 7 she received 130 mg. of chlorambucil, with little response, and on Feb. 7 she was given HN2, 20 mg. intravenously in a single dose, with some relief of pain. Between Feb. 14 and March 15 she had a second course of 300 mg. of chlorambucil, but her nodes enlarged during this treatment and she became febrile and moderately ill. Accordingly, on both March 18 and 25 she was given 20 mg. of HN2 intravenously, without response, and on March 26 she began a course of radiation to the left neck and supraclavicular area. She responded dramatically, so far as pain was concerned, to a tumor dose of 2700 r (200 kv., 1.0 Cu HVL). However, on April 30 she required 20 mg. of HN2 intravenously and 10 mg. intrapleurally because of marked constitutional symptoms and pleuritic pain. Cultures for acid-fast organisms were taken at that time and were later reported as negative. By May 7 the patient was severely ill and required an oxygen tent for respiratory distress: another dose of 20 mg. of HN2 was given intravenously on that date, since x-ray of the chest showed extensive bilateral infiltration and large pulmonary parenchymal masses. On May 22 she spontaneously delivered a normal 5 lb. 1 oz.

female infant, improving enough thereafter to permit her discharge from the hospital on May 31. However, the patient deteriorated rapidly during the following month and died on July 1, 1957. At autopsy there was not only marked pulmonary involvement with Hodgkin's disease but also far-advanced pulmonary tuberculosis. The baby was well when seen two months post partum.

Comment.—In the second and third trimesters of her pregnancy this patient had a total of five doses of 20 mg. of HN2 intravenously, plus two courses of chlorambucil of 130 mg. and 300 mg., 10 mg. of HN2 intrapleurally, and 2700 r of irradiation. The problem in this case was intractable pain of such severity that lobotomy was seriously considered. However, the pain responded to irradiation.

CASE 17.—A 19-year-old woman developed right cervical adenopathy in April, 1954, with easy fatigue and a 20 lb. weight loss over the next eight months. In November, 1954, biopsy of a cervical node led to the diagnosis of Hodgkin's disease, and the patient was given radiation therapy, with tumor doses of 1034 r to the mediastinum and 1188 r to the right neck. The patient went into remission until May, 1956, when she developed generalized pruritus. She became pregnant for the first time in June. On Dec. 20, 1956, she was admitted to Walter Reed Army Hospital with severe pruritus and recurrent cervical and mediastinal nodes, in general good health, and was given 378 mg. of chlorambucil between Dec. 21 and Jan. 11, in the seventh month of pregnancy. Her response was excellent, with relief of itching and shrinkage of the cervical nodes but without apparent change in the mediastinal nodes. The patient went into remission, which lasted until after delivery of a normal infant, March 13, 1957, at term. However, following delivery she again developed pruritus, with an increase in the size of her cervical and mediastinal nodes. She responded so poorly to a second course of chlorambucil, 330 mg. between April 11 and May 16, that she required radiation therapy, receiving tumor doses of 3570 r to the mediastinum and 2548 r to the left supraclavicular area. At present, 10 months post partum, the baby is in excellent health, but the mother is pregnant again, in exacerbation with a large mediastinal mass and the threat of atelectasis; we are again faced with the problem of treatment in pregnancy.

Comment.—The problem in this case was intractable itching, which responded to treatment of Hodgkin's disease with chlorambucil.

CASE 18 (Case 3 of Heaton et al.[73]).—A 22-year-old white woman noticed a painless supraclavicular tumor in the spring of 1953, in the seventh month of pregnancy. Two months after the delivery of a normal child this mass had enlarged; she became febrile, and mediastinal masses were demonstrated on x-ray. Biopsy of a cervical node led to the diagnosis of Hodgkin's disease, and the patient was given roentgen therapy to the mediastinum and neck. In December, 1954, inguinal and intrapelvic nodes appeared. It was unsuspected that the patient was in the first month of pregnancy, and she was treated with 16 mg. of triethylene melamine during eight days, with regression of these nodes. Her pregnancy proceeded uneventfully to term, with delivery of a normal infant. However, following delivery she again required radiation to the neck and mediastinum. She remained well thereafter until the fall of 1955, when she developed an osteolytic lesion of the fourth lumbar vertebra, with weakness and paresthesias of the lower extremities. These symptoms disappeared following radiation to the spine as well as to recurrent inguinal, cervical, and retrogastric nodes, to which she reacted rather severely. The patient's symptoms recurred in March, 1956, when she received radiation to the abdomen and a course of 25 mg. of triethylene melamine. She developed marked marrow depression, and splenectomy was performed. After this, the patient improved sufficiently to be discharged on April 30, 1956.

Comment.—This case is particularly interesting, since the patient was given 16 mg. of triethylene melamine in the first month of pregnancy without ill effect. The patient reported by Wright et al. (Table 1), had a much larger dose than this, both in courses and in maintenance, with two spontaneous abortions. The total dose that their patient received is uncertain but was certainly far in excess of a single course of 16 mg. in eight days.

CASE 19.—This 22-year-old white woman developed a cough and tender axillary nodes in April, 1954. The diagnosis of acute granulocytic leukemia was made at another hospital, where the patient was treated with transfusions and placed on cortisone for a two-week trial. On May 19 she was transferred to Walter Reed Army Hospital, arriving with nausea, vomiting, abdominal pain, and a low-grade fever, with generalized shotty lymphadenopathy and splenomegaly. Her initial white cell count here showed 260,000 white cells, with 95% blast cells. On May 20 the patient was started on mercaptopurine, 150 mg. daily, and cortisone, 100 mg. daily, with clinical improvement

and a fall in her white cell count to 5000 cells by May 28. On June 15 she was discharged to outpatient follow-up, on mercaptopurine, 75 mg. a day, and cortisone, 50 mg. a day, on which she did fairly well. However, in August her weakness and malaise returned, and she was readmitted Aug. 28 with submaxillary nodes, splenomegaly, and mediastinal widening, with a white cell count of 127,000 with a preponderance of immature forms. She continued on the same dose of mercaptopurine and cortisone. On Sept. 8 the diagnosis of early pregnancy was confirmed. On Oct. 14, because of a lack of response to her other drugs, she was started on aminopterin, with 2 mg. a day for two days and 1 mg. daily thereafter for five days. On Oct. 18 she began a course of 4 gm. of cortisone a day for five days, with a decrease to 100 mg. daily after the initial 20 gm. On Nov. 10 she began 200 mg. a day of mercaptopurine. By mid-November she was somewhat improved, but on Nov. 19, because of a marked fall in platelet count, the mercaptopurine was discontinued and the cortisone was reduced to 50 mg. daily. Since her disease remained active, she was given 10 mg. of demecolcine on Dec. 7, 10, 13, and 24 but continued to do very poorly. The patient was given mercaptopurine, 50 mg. a day, but the nodes in the neck enlarged markedly, the spleen enlarged to a level just above the pubis, and she developed ecchymoses of the legs. By late December she was acutely ill, with high swinging temperatures, and on Jan. 9 she spontaneously aborted. The fetus weighed 1 lb. 9 oz. and lived for 19 hours with vigorous support; there were no malformations. After delivery aminopterin, 0.5 mg. daily, was added to the patient's other medications, but she continued to go rapidly downhill and died on Jan. 14, 1955.

Comment.—The point of particular interest in this case is that the mother conceived while on 75 mg. of mercaptopurine daily, and despite large doses of mercaptopurine, plus demecolcine, aminopterin, and large doses of cortisone, carried her pregnancy far into her terminal illness and produced a fetus capable of living 19 hours, though weighing only 1 lb. 9 oz.

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The Oxidative Activity of Blood Serum in Schizophrenic and Manic-Depressive Psychoses

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Oxidative processes in schizophrenia are currently being studied in many laboratories because some authors have speculated that hallucinations and other symptoms of schizophrenia might be caused by substances produced during possibly abnormal oxidation of epinephrine in schizophrenic patients. Akerfeldt [1] recently described a test that measures the oxidative power of serum; this test depends on the time that it takes for a red color to appear in serum after the addition of N,N′-dimethyl-*p*-phenylenediamine, a substance that turns red when oxidized. Akerfeldt reported that serum from schizophrenic patients oxidized this substance very rapidly, whereas serum from normal subjects oxidized it slowly. However, he also noted that both normal pregnancy and chronic infection likewise caused abnormally rapid oxidation of N,N′-dimethyl-*p*-phenylenediamine. Nevertheless, some observers have accepted the test as useful in the diagnosis of mental disease. On the other hand, Horwitt et al.[2] found the test to be without value, and Angel et al.[3] found that the oxidation was accelerated only in early and not in chronic cases.

Akerfeldt further claimed that his test must be a valid measure of serum ceruloplasmin concentration, in view of the fact that the oxidative power of blood serum is due to the presence of ceruloplasmin [4]; Abood [5] concurred in Akerfeldt's belief. However, the fact is that serum oxidative power *as measured* is the resultant of ceruloplasmin activity on the one hand and the reducing activity of such substances as ascorbic acid on the other.

Studies recently made in this laboratory show that the Akerfeldt test does not measure serum ceruloplasmin *concentration* and is not useful in the diagnosis of mental or other diseases. The test does measure oxidizing activity, but in any case this activity is subject to large variations caused by changes in the concentration not only of ceruloplasmin but of other substances, notably ascorbic acid.

The Akerfeldt Test as a Measure of Ceruloplasmin Concentration

When the studies of the Akerfeldt test were begun here, the test was first standardized with respect to the temperature and the pH at which it was carried out.[6] This was necessary because Akerfeldt had not standardized the procedure, and consequently uncontrolled variables, such as temperature and hydrogen-ion concentration, caused aberrations in the results.

The mixture of serum and reagent used in Akerfeldt's original test, and in the standardized version developed in this laboratory,[6] is such that the amount of the substrate always limits the rate of the reaction. Since the amount of serum used can never be the limiting factor, the test as thus far formulated cannot measure serum *ceruloplasmin content*. However, if the assumption is made that the ceruloplasmin and the various other active substances in the serum act catalytically and hence in accordance with Michaelis-Menten enzyme kinetics, comparison of *maximal* oxidizing velocities per unit of substrate obtained with different sera should afford an indication of relative

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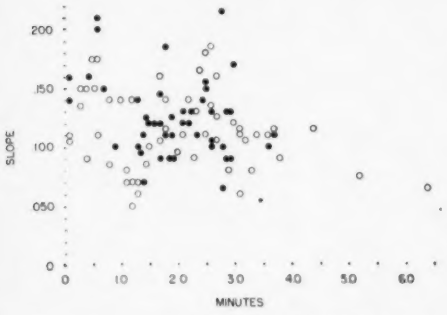

Fig. 1.—Appearance time of color plotted against slope (i. e., maximal activity) of the Akerfeldt reaction. Dots represent data in schizophrenic or manic-depressive patients; circles represent data in normal subjects.

oxidizing power, which is the resultant of the oxidation due to the presence of ceruloplasmin and the inhibition of the oxidation due to the presence of other substances. If the concentrations of these inhibiting substances in serum were invariable, the test could be used to indicate *relative ceruloplasmin activity*. However, at least some of these substances vary from patient to patient and also in the same patient from time to time. Accordingly, the test does not measure either *ceruloplasmin content* or *relative ceruloplasmin activity*. Moreover, there is no correlation between the appearance time of the color and the *maximal* velocity of the reaction as measured by its slope (Fig. 1), and hence the use of only the appearance time as the critical measurement of the test cannot provide an index of relative oxidative activity.

Variations in Serum Oxidizing Activity Caused by Administration of Ascorbic Acid

Akerfeldt stated that the development of color in his test probably occurs as follows:

1. The N,N′-dimethyl-*p*-phenylenediamine is oxidized to a colored semiquinone by ceruloplasmin in the plasma; this reaction proceeds in a linear fashion.

2. The colored semiquinone is immediately reduced by the ascorbic acid in the plasma.

3. The ascorbic acid is consumed, and then the N,N′-dimethyl-*p*-phenylenediamine is again oxidized to the colored semiquinone. Some of the latter is reduced by other inhibitors in the serum, and hence the reaction from this point on is not linear.

Akerfeldt's theoretical explanation of the reaction underlying his test suggests that the quantity of ascorbic acid present in the serum might greatly affect results obtained with the test. In order to investigate this possibility, 14 subjects were given orange juice or ascorbic acid, in addition to their normal diet, as follows:

1. Each of five normal subjects received 1.5 liters of orange juice over a period of 18 hours.

2. Each of five normal and four psychotic subjects received 1.0 gm. of ascorbic acid in three doses of 250, 250, and 500 mg., respectively, over a period of 18 hours.

The Akerfeldt test as modified in this laboratory [6] was carried out in each subject before, and again 24 hours after, the first dose.

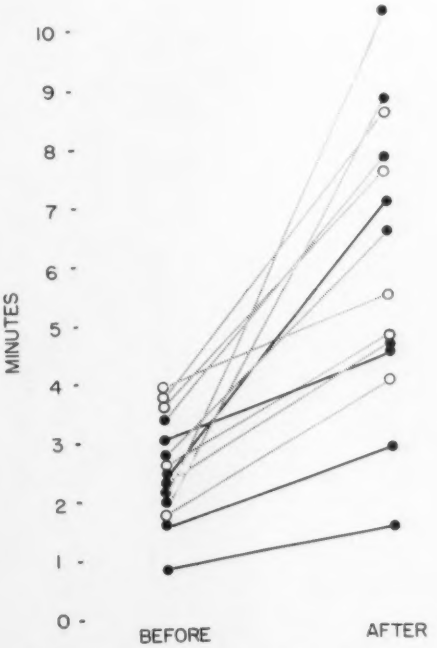

Fig. 2.—Effect of ingestion of orange juice or ascorbic acid on appearance time of color. Circles indicate data in psychotic patients; dots indicate data in normal subjects. Solid lines indicate experiments with orange juice; dotted lines indicate experiments with ascorbic acid.

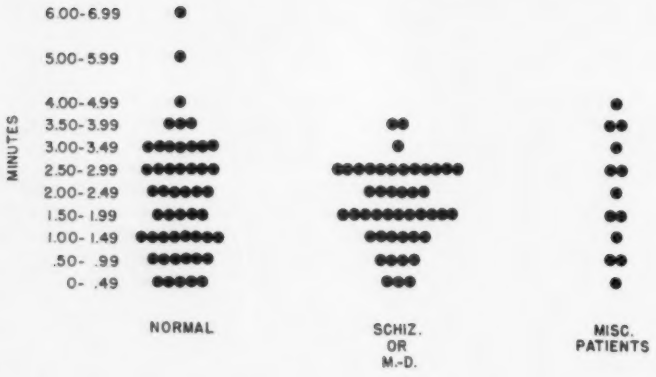

Fig. 3.—Appearance time of color in the Akerfeldt reaction in normal subjects, schizophrenic or manic-depressive patients, and other hospitalized patients.

In every instance the red color developed more slowly in sera drawn after the ingestion of orange juice or ascorbic acid than in the control sera; i. e., the measured serum oxidative power decreased after administration of those substances (Fig. 2). The average time of appearance of color was 2.7 minutes in control sera and 6.1 minutes in sera obtained after the ingestion of orange juice or ascorbic acid.

It is evident that the nutritional state of the subject largely determines the result of the test.

Lack of Value of the Akerfeldt Test in the Diagnosis of Mental Disease

The standardized test developed in this laboratory [6] was carried out 109 times on the sera of 101 subjects; these included 46 healthy normal students, nurses, and hospital employees; 43 schizophrenic or manic-depressive patients, of whom 41 were chronically psychotic, and 12 hospital patients who did not have schizophrenic or manic-depressive psychoses but were suffering from neurosis, alcoholism, or senile brain disease. The rapid color appearance that Akerfeldt considers diagnostic of mental disease was found no more frequently in sera drawn from patients than in those obtained from the normal subjects (Fig. 3). The average and median times of color appearance were 1.8 and 2.0 minutes, respectively, in the normal subjects and 1.9 and 1.9 minutes in the schizophrenic and manic-depressive patients. Similarly, use of the slopes of the curves of color development as an index of the maximal oxidizing activity revealed no differences between sera obtained from normal subjects and those drawn from psychotic patients (Fig. 1).

The Akerfeldt test affords no evidence that serum oxidizing activity is abnormal in chronic schizophrenic or manic-depressive psychoses.

Comment

Akerfeldt suggested that increased concentrations of plasma ceruloplasmin and decreased concentrations of plasma ascorbic acid occurred in schizophrenic and manic-depressive psychoses and that both these biochemical changes, acting together, accounted for the rapid oxidation of N,N′-dimethyl-*p*-phenylenediamine that he described in sera drawn from psychotic patients. Accordingly, he [1] and others [5] believed that the test measured *ceruloplasmin concentration* or at least *relative ceruloplasmin activity*.

Although the Akerfeldt test can be made to measure crude oxidative activity, it cannot measure *ceruloplasmin concentration* or *relative ceruloplasmin activity*. Moreover, there is no evidence that ceruloplasmin content is regularly elevated in chronic schizophrenic or manic-depressive psychoses: Markowitz et al.[7] found it to be increased in only 1 of

3 schizophrenic patients, and Scheinberg et al.[8] found it to be above the normal range in only 3 of 20 such patients.

Ceruloplasmin contains copper; indeed, 75% to 95% of the copper in plasma is bound in ceruloplasmin. Accordingly, measurement of plasma copper level yields some information about plasma ceruloplasmin concentration. Munch-Petersen[9] found normal plasma copper levels in his schizophrenic patients, and Markowitz et al.[7] found the level normal in two of their three cases; Horwitt et al.[2] and Angel et al.[3] found it within the normal range in most instances. Brenner and Breier[10] and Hielmeyer et al.[11] reported high values in most of their patients. Perhaps the differences among these authors with respect to plasma copper levels can be traced to variations in the incidence of intercurrent diseases (many of which elevate plasma copper levels) in their patients. Indeed, Munch-Petersen[9] and Horwitt et al.[2] actually correlated high plasma copper levels with laboratory evidence of infection. Chronicity, or lack of it, might have been another factor that caused the differences.

Similarly, a low plasma ascorbic acid concentration is not characteristic of uncomplicated schizophrenia. Although low plasma ascorbic acid values are found in some patients,[2,12-16] particularly those recently admitted to hospitals, these low levels are rapidly restored to normal when ascorbic acid is given.[14,15] Most authors agree that such low values are due to malnutrition and not to the schizophrenia itself; the incidence of low plasma ascorbic acid values in chronically hospitalized psychotic patients depends on the size of the food budget and the adequacy of the personnel. The findings of Friedlander et al.[17] and the results of plasma ascorbic acid measurements made at this hospital[18] in chronically schizophrenic patients proved that low levels are not characteristic of the disease.

The foregoing considerations show plainly that there is no reason to expect to find enhanced serum oxidative activity in uncomplicated schizophrenic and manic-depressive psychoses. Measurements of serum oxidative activity made in this laboratory revealed no difference in oxidizing power between sera obtained from normal subjects and those obtained from patients with chronic psychoses. These findings are in agreement with those of Markowitz et al.[7] and of Horwitt et al.[2]; the data are also in harmony with those of Leach and Heath[19] and of Angel et al.,[3] who reported that plasma oxidative activity may be high in acute cases (i. e., those in whom malnutrition commonly occurs) and not in chronically hospitalized patients. The finding of increased oxidative activity in the serum of schizophrenic patients reported by Akerfeldt[1] and by Abood et al.[5] was probably due to malnutrition in the subjects studied by those workers. The evidence at hand may be summarized to the effect that both plasma oxidative activity and ceruloplasmin content are normal in uncomplicated chronic schizophrenic or manic-depressive psychoses, although the oxidative activity may be increased in malnourished patients. It is evident that increased plasma oxidative activity is not an essential feature of, and thus is not diagnostic of, these psychoses. This fact does not, of course, exclude the possibility that other oxidative systems may be abnormal in schizophrenic and manic-depressive psychoses.

Summary and Conclusions

Measurement of serum oxidative activity by means of a modification of the Akerfeldt test revealed no abnormalities in the sera of patients with chronic schizophrenic or manic-depressive psychoses. The data presented here and the other considerations discussed in this paper show that increases in plasma oxidative power or in ceruloplasmin concentration or activity are not characteristic of these diseases.

The Akerfeldt test does not measure serum ceruloplasmin content, and even though it can be made to measure oxidative

activity, the latter is so subject to variations in plasma ascorbic acid level, owing to both dietary factors and disease, as to make it impossible to use the Akerfeldt test to diagnose any specific condition.

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Case Reports

Cryptococcal Meningitis Treated with Amphotericin B

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Cryptococcosis, in common with many fungal diseases, remains a difficult problem due to the lack of an effective therapeutic agent.[1-4] Reports of new antifungal drugs, notably nystatin and Actidione,[3,5-8] have helped to stimulate interest in this disease. Amphotericin B, a recently isolated derivative of a streptomycete,[9-11] has shown promise in the therapy of several fungal diseases, including cryptococcosis. Reports of clinical trials are few; Appelbaum and Shtokalko [12] illustrated the arrest of cryptococcal meningitis with Amphotericin B, though evaluation of therapy is difficult in a disease known for spontaneous remissions.[1,2,13-15]

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The following case of cryptococcal meningitis treated with amphotericin B, but ending fatally in spite of clearing the spinal fluid of organisms, is presented to add to the clinical experience in the use of this drug.

Report of Case

A 32-year-old housewife was first admitted to St. Mary's Hospital on Oct. 8, 1956, for delivery of a healthy full-term boy. Six weeks prior to admission, she noted a "pimple" on her right cheek, which later became ulcerated.

Physical examination was not remarkable for a full-term pregnancy, except for the lesion on the right cheek, which was 0.75 cm. in diameter and had a rolled indurated border with an ulcerated center, mild crustation, and several small bleeding points. This was excised widely, and pathological sections revealed encapsulated organisms characteristic of Cryptococcus neoformans (Fig. 1). The patient was asymptomatic and was discharged.

Fig. 1.—Section of skin lesion, showing numerous cryptococci; reduced 15% from mag. × 100.

On Nov. 2, 1956, the patient was readmitted, complaining of headaches, blurred vision, and stiffness of the neck occurring two weeks prior to admission. Physical examination revealed a blood pressure of 120/60; pulse, 90; temperature, 99.4 F orally; respirations, 22. She was well oriented and cooperative. There was a well-healed scar on the right cheek, moderate nuchal rigidity, and sixth cranial nerve palsy on the left; the remainder of the physical examination was within normal limits.

Examination of blood revealed a white cell count of 8050, with 6 stab cells, 80 neutrophils, 9 lymphocytes, 2 monocytes, and 3 eosinophils; hemoglobin, 14.0 gm. %; hematocrit, 40 vol. %; erythrocyte sedimentation rate, 2 mm. in one hour. The urine was within normal limits. VDRL was reactive; the Kahn and Kolmer tests, however, were nonreactive. Spinal fluid was clear, with an opening pressure of 200 mm. of water. There were 54 cells, predominantly mononuclear; sugar was 43 mg. %; protein, 84 mg. %, and chloride, 145 mEq. per liter. Smear with India ink revealed numerous encapsulated budding organisms, which on culture produced smooth, creamy, orange-colored colonies within 24 hours at 37 C and at room temperature. Mice given intraperitoneal injections with culture material succumbed to cryptococcosis within three to four weeks. Negative skin tests were obtained with purified protein derivative of tuberculin (P. P. D.), histoplasmin, coccidioidin, and blastomycin. Sputum and stool cultures were negative for cryptococci. Chest x-ray was within normal limits.

On Nov. 3, 1956, the patient was begun on sulfadiazine as a lipoid suspension, 1 gm. three times daily; saturated solution of potassium iodide, 10 drops four times a day, and sodium bicarbonate, 10 gm. three times daily. The patient became asymptomatic within 10 days. She then was discharged on Nov. 17, 1956, on sulfadiazine and potassium iodide.

On Jan. 2, 1957, the patient was readmitted because of recurrence of severe frontal and bitemporal headaches, blurred vision, nausea and vomiting, and weakness in the lower extremities of approximately one week's duration.

Physical examination revealed a blood pressure of 130/70; pulse, 62; temperature, 99.5 F orally, and respirations, 20. She was cooperative, oriented, but mildly obtunded. A 3 mm. in diameter erythematous papular lesion with a pinpoint hemorrhagic center was located just superior and lateral to the right naso labial fold. A smaller similar lesion was superimposed on the scar from previous excision. Nuchal rigidity was moderate. Weakness of the left lateral rectus was present; the pupils reacted well to light and accommodation. The eyegrounds revealed hemorrhages, papilledema, and evidence of optic atrophy. In addition, there was weakness of the right seventh cranial nerve peripherally. The heart and lungs were within normal limits. There was weakness to flexion of the right leg, but otherwise no diminution of strength or range of motion of the extremities was demonstrated. The deep tendon reflexes were moderately depressed, as were the abdominal reflexes.

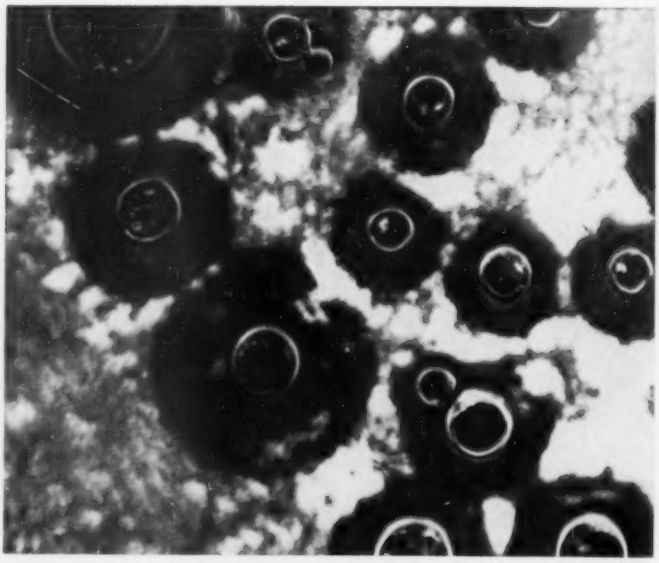

Fig. 2.—Noncentrifuged spinal fluid in January, 1957, showing numerous budding encapsulated C. neoformans; reduced approximately 20% from mag. × 2000.

Laboratory data included a white blood cell count of 5950, with 3 stab cells, 77 neutrophils, 17 lymphocytes, 2 monocytes, and 2 eosinophils. Hemoglobin was 13.5 gm. %; hematocrit, 40 vol. %. Urinalysis was within normal limits. VDRL was again noted to be reactive, as were the Kahn and Kolmer tests. Serum sodium, chloride, potassium, carbon dioxide-combining power, nonprotein nitrogen, fasting blood sugar, cephalin-cholesterol flocculation, and thymol turbidity were within normal limits. Cloudy spinal fluid with an opening pressure in excess of 850 mm. of water disclosed on India ink preparation numerous encapsulated budding organisms typical of C. neoformans (Fig. 2). Sugar was 12 mg. %; proteins, 146 mg. %; chlorides, 115 mEq. per liter. The colloidal gold curve was 0000542100. The Kolmer test was nonreactive. Culture again revealed creamy orange-colored colonies within 24 hours at 37 C. In addition, scrapings of the facial skin lesions were cultured and revealed cryptococci identical to those recovered from the spinal fluid.

Sulfadiazine suspension was increased to 6 grams daily; blood levels were maintained between 20 and 25 mg. %. In the next two weeks, the patient became increasingly lethargic and her eyes became mildly proptosed. Hearing became impaired bilaterally, and the right facial nerve palsy was more marked; deep tendon reflexes became generally sluggish. Because the patient was obviously deteriorating on sulfadiazine (300 gm. over a 12-week period) and iodides, amphotericin was begun. Therapy was given in gradually increasing dosage, with a maximum of 1.5 mg. per kilogram (90 mg.) in 500 cc. of 5% dextrose in water, intravenously, over a four- to six-hour period.

Between Jan. 18 and Jan. 29, 1957, she received 800 mg. of amphotericin B. During this period the facial lesions healed completely (repeated scrapings were negative by smear and culture). Between Feb. 1 and Feb. 18, 1957, an additional 1590 mg. of amphotericin was given. The patient remained asymptomatic, and the spinal fluid became crystal clear under decreasing pressure, though organisms remained demonstrable by smear and culture (Fig. 3). Papilledema had decreased, though optic atrophy resulted in a limitation of vision to light perception. All therapy was discontinued on Feb. 18, 1957, because of a leukopenia (white blood cell count of 2400, with normal differential) and anemia (hemoglobin of 8.5 gm. %).

By Feb. 28, 1957, blood cell counts reached near normal and amphotericin B alone was restarted, with a dosage of 60 mg. daily. On March 10, 1957, therapy was withdrawn because of recurrent severe headaches during the infusion. She had received a total of 3050 mg. The last course was otherwise well tolerated, with no significant change in peripheral blood cell counts, and the spinal fluid for the first time was sterile with normal manometrics.

Headaches persisted, however, and on March 15, 1957, the patient became disoriented. On the basis that she had developed arachnoiditis, steroid therapy, with use of corticotropin zinc and prednisone, was begun. One week later, the patient was mentally alert, with an increased appetite and mild euphoria. Between March 26 and April 16, 1957, an additional course of 630 mg. of amphotericin B (total 3680 mg.) was given; steroids were gradually withdrawn by April 13, 1957. There were no untoward effects noted at this time, and spinal fluid remained sterile.

On April 24, 1957, the patient suffered a grand mal convulsion; the spinal fluid became xanthochromic, and six days after inoculation of media, one colony of cryptococci appeared. However,

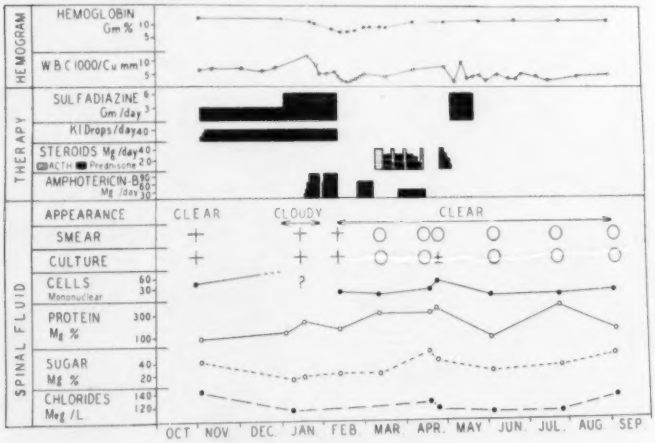

Fig. 3.—Graphic representation of clinical course. Note repeated effect on white cell count with sulfadiazine and clearing of spinal fluid after amphotericin B.

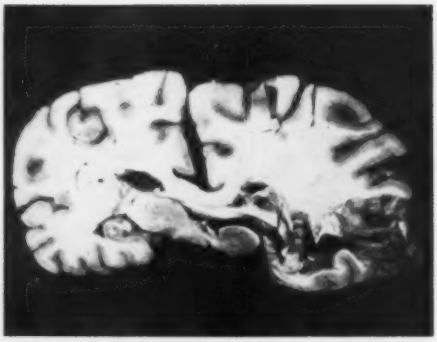

Fig. 4.—Transverse section of brain. Note mass of cryptococci in left hemisphere, producing internal hydrocephalus. Organisms taken from this lesion failed to reproduce on artificial media and were not pathogenic for mice.

three subsequent examinations were negative by smear and culture. With the patient taking diphenylhydantoin (Dilantin), 60 mg. three times daily, no subsequent seizures were noted. Steroids were given for one week, followed by slight improvement. Between May 5 and May 23, 1957, seventy grams of sulfadiazine was given, and again a transient leukopenia appeared.

During June and July, the patient became mildly obtunded, though she continued to eat well and was ambulatory. Recent and remote memory gradually deteriorated. During the last week of August, the patient became increasingly lethargic and eventually semicomatose. On Sept. 4, 1957, Cheyne-Stokes respirations were observed, and on the evening of that day, she quietly died.

Postmortem examination disclosed diffusely flattened gyri, with multiple focal collections of yellow cloudy material in the subarachnoid space. Marked softening was noted over the posterior aspect of the left temporal lobe. Section of the brain in its transverse axis (Fig. 4) revealed a 2×2 cm. firm white gelatinous mass obstructing flow of cerebrospinal fluid from the left lateral ventricle; the posterior horn had dilated spherically, measuring 4×4 cm., resulting in compression of surrounding brain tissue. The remainder of the brain was diffusely edematous. Microscopically, the gelatinous mass was composed of necrotic tissue and numerous cryptococci (Fig. 5). Surrounding this mass was a minimal glial response with marked lymphocytic infiltration. Sections thru the dilated horn revealed an intact ependyma, though an occasional Cryptococcus was seen in the irregular frayed cerebral tissue surrounding this area. The peripheral cortex revealed thickened pia and arachnoid tissue infiltrated with numerous lymphocytes and cryptococci. The cerebellum and spinal cord were similarly involved; several organisms were seen in the cord substance without cellular response (Fig. 5). The pituitary was entirely normal.

The lungs appeared normal grossly. However, numerous firm circumscribed discrete masses 0.5 to 1.0 cm. in diameter and slate blue in color were seen throughout subpleural and central areas. The hilar nodes did not appear unusual. Microscopically, the discrete masses were well-circumscribed lymphoid tissue with scattered anthracotic pigment. Chronic inflammatory cells were noted about the masses and in the alveoli immediately surrounding them. No cryptococci were seen either in the lymphoid areas or in the lung parenchyma. The hilar nodes were anthracotic but otherwise not remarkable.

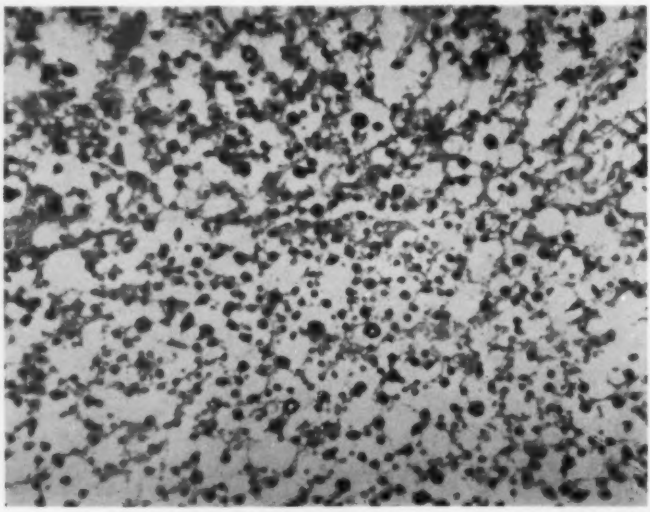

Fig. 5.—Section of gelatinous mass near left lateral ventricle, revealing cryptococci and necrotic cerebral tissue; reduced 15% from mag. × 300.

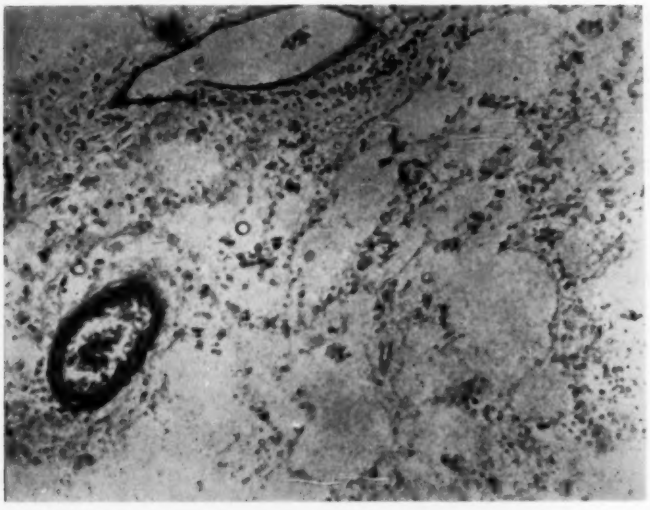

Fig. 6.—Section of spinal cord. Note cryptococci near arteriole; reduced 15% from mag. × 300.

The liver was mildly congested; the spleen and kidneys were not remarkable. The adrenals disclosed no evidence of lipoid depletion. The bone marrow was entirely within normal limits. No cryptococci were seen outside of the central nervous system.

Of pertinent interest is the apparent alteration of the organisms found at autopsy. Fresh brain tissue containing numerous cryptococci was injected into mice, and up to the time of this writing (Jan. 9, 1958) the animals appear quite healthy; nor have the organisms grown on artificial media.

Comment

It appears fairly obvious that the disease process had reached an advanced state before amphotericin was started. We believe evidence of effective therapy may be based on clearing of the skin lesions one week after amphotericin was started, sterilization of the spinal fluid after less than two months of therapy, and apparent alteration in pathogenicity to mice and growth on artificial media. Perhaps earlier therapy would have altered the outcome for the patient.

Steroid therapy was used in the hope of preventing mechanical obstruction of circulatory channels of cerebrospinal fluid by exudate formation and to avoid formation of avascular tissue which would prevent drugs from reaching the organisms enmeshed therein. This is essentially its rationale in exudative forms of meningitis,[16,17] notably tubercular. The dangers of steroid therapy in cryptococcosis have been documented.[18]

Apparently the gelatinous mass in the left lateral ventricle of the brain of this patient is typical of early tissue changes from cryptococcal meningitis. Later changes are said to be of a more granulomatous nature.[19-23] The typical subpleural nodules seen in cryptococcosis have been previously described.[23]

We do not feel the toxicity of amphotericin B demonstrated in this patient precludes its use. The observed bone marrow depression was most likely due to sulfadiazine, particularly in view of the high blood levels employed, and repeated leukopenia when sulfadiazine alone was used. Acute toxicity, consisting of fever, nausea and vomiting, and severe headaches, was difficult to evaluate in view of the symptoms present prior to therapy. Control with symptomatic drugs was adequate. Thrombophlebitis was not a factor in this case.

Summary

A case of cryptococcal meningitis treated with amphotericin B ended fatally despite clearing of the spinal fluid of organisms.

Cryptococcal dermatitis, recurring after excision and sulfadiazine-iodide therapy, healed completely after seven days' therapy with amphotericin.

Loss of pathogenicity and reproductive capacity of cryptococci was demonstrated after amphotericin therapy.

Toxicity to amphotericin was negligible in this patient.

Dr. Peter Soto, Dr. Leonard Laskowski, and the Department of Pathology of St. Louis University, under Dr. Henry C. Pinkerton, aided in preparing material for this report.

This case was included in a report of "Cryptococcosis with Cutaneous Manifestations" by Morris Moore, Ph.D., in *J. Invest. Dermat.* 28:159, 1957.

Amphotericin B was supplied by Dr. Gavin Hilkick-Smith, of the Squibb Institute for Medical Research, New Brunswick, N. J.

Sulfadiazine suspension was supplied by the Donley-Evans Co., St. Louis.

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An Agent Effective Against Cryptococcosis of the Central Nervous System

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Introduction

In 1950, Mosberg and Arnold reviewed all reported cases of cryptococcosis.[1] In summarizing results with more than 25 therapeutic agents, they concluded that "no methods of treatment have proved effective . . . any encouragement provided by an apparent response to a drug is in most cases nullified by an equally discouraging response when the same drug is employed on another patient."

In 1952, Carton[2] summarized the approximately 200 reported cases of cryptococcosis with central nervous system involvement with the statement that of the 14 patients alive at the time of their respective reports only 1 could be considered cured. (This patient was well and apparently free of infection six years after treatment with sulfadiazine.[3]) Carton then summarized the previously reported experiences with cycloheximide (Actidione, Upjohn), including seven fairly well documented cases, by saying "the use of Actidione in the central nervous system disease has been unsatisfactory, except for an occasional case; no infection has been cured . . ." Of the four personal cases which he then reported, he considered one apparently neurologically and mycologically cured two and one-half months after cessation of treatment and another definitely improved. This did not alter his general conclusion that "Actidione is not very effective against central nervous system cryptococcosis."

In February, 1956, Dr. Louis Boshes and his associates published their timely discussion of fungus infections of the central nervous system.[4] They reported three cases of cryptococcosis treated with cycloheximide, still considered the most promising drug. Two of the patients died in spite of the drug, and the third died possibly because of the drug. After reviewing their own results as well as all others published, the authors concluded that "the clinician remains powerless in most instances in the management of fungus infections [of the central nervous system]."

In 1956, Gold and others reported the isolation from soil obtained from the Orinoco River region of Venezuela of a streptomycete culture possessing antifungal activity.[5] They attributed this activity to two related antibiotics, amphotericins A and B, which were isolated in crystalline form and analyzed by Vandeputte and associates.[6] These substances were shown to be active against Cryptococcus neoformans infections in mice, amphotericin B exhibiting greater inhibitory effect than amphotericin A in corresponding concentrations.[7] The former was active in concentrations well within the toxicity tolerance of mice.[11]

Shortly after these reports appeared, we had an opportunity to observe the clinical efficacy of amphotericin B.

Report of Cases

CASE 1.—A 32-year-old man entered the Veterans' Administration Research Hospital in May, 1955, with nausea, vomiting, anorexia, and right-sided headaches. He had been well until about six weeks previously, when he noted the gradual onset

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From the Department of Neurology and Psychiatry and the Department of Surgery, Northwestern University Medical School, and the Neuropsychiatric Service, Veterans' Administration Research Hospital.

of pain and a sense of swelling in the right frontal region. There were associated joint pains, malaise, and symptoms of upper respiratory infection. About 10 days after his discomfort began, there was a sudden popping sensation in the right forehead followed by drainage of amber foul-smelling material from his nose and prompt relief of his headache. About a week later, however, his headache recurred and he entered a nearby hospital. When he overheard a discussion to the effect that brain abscess was likely, he left the hospital and came to Chicago. Under suspicion of a space-occupying intracranial lesion, he was admitted to the neurosurgical service.

On admission, neurological examination was normal. Skull films revealed a large area of decreased density in the left frontal bone. An air study was normal. The cerebrospinal fluid contained 405 cells per cubic millimeter, all lymphocytes. Total protein was 95 mg. % and glucose was 37 mg. %. Left carotid angiography revealed posterior displacement of the anterior cerebral artery. Left frontal trephination disclosed a cyst which was drained of 50 to 100 cc. of clear, colorless fluid. Culture of the fluid was negative for bacteria and fungi. He was discharged with partial relief of his symptoms and remained improved until the first part of 1956, when the symptoms became as severe as before.

By the time of readmission in April, 1956, he had lost 20 lb. Initially, blurring of the margins of the right optic disk was the only neurological finding, though he appeared questionably lethargic and alternately seemed very anxious or surprisingly unconcerned. An air study was again normal. Left carotid angiography was technically unsatisfactory, and right carotid angiography was normal. The patient then began to have brief episodes of strabismus with diplopia. The neurology consultant found right facial weakness and, in the upper extremities, tremor and decomposition of movement. He could elicit no history indicating exposure to specific fungus or virus infection but recommended transfer to the neurology service for serial spinal fluid examinations. On May 25, 1956, spinal fluid cell count was 24, all lymphocytes. Sugar was 13.3 mg. %. At this time the patient's condition took a striking turn for the worse, manifested especially by progressive somnolence and mental deterioration. On May 29, in an India ink preparation of fresh spinal fluid, rare encapsulated yeast forms were first found and tentatively identified as C. neoformans. Although cultures initially showed no growth, it was decided that treatment could not await such confirmation, and cycloheximide therapy was started. By the second week in July, after five weeks of treatment with a dosage of 40 mg. intramuscularly every six hours, the patient was stuporous to comatose at all times. Temperature varied between 101 and 104 F. There was nuchal rigidity and opisthotonos. Respirations were largely of the Cheyne-Stokes type. All examiners agreed that death was imminent.

Amphotericin B * was first given by nasogastric tube on July 12, 1956. At that time the spinal fluid sugar was 8 mg. %. Treatment was interrupted after 13 days because of apparently deepening coma and persistence of marked nuchal rigidity. We were intrigued to note, however, the recurrence of hiccough, which had first appeared shortly before the drug was started but had vanished during the course of therapy. A report of spinal fluid sugar of 29 mg. % further encouraged us to reinstitute therapy. Again the hiccough stopped. At about this time there appeared progressive lower extremity weakness of the flaccid type, and on Aug. 26 the patient was found to have a markedly distended bladder, which required indwelling catheter drainage.

Within a week after the second course of amphotericin was started there appeared a definite improvement in the patient's state of consciousness, accompanied by a decrease in both nuchal rigidity and fever. He began to converse with members of his family, and on Sept. 11, for the first time in four months, he recognized one of his physicians and called him by name. Minimal voluntary motion returned in his lower extremities, and the catheter was removed without recurrence of urinary retention.

After six successive spinal fluid cultures had been reported positive for C. neoformans, that of Aug. 14 was reported negative. On Sept. 11, two months after therapy was started, spinal fluid sugar was 63 mg. %, the first normal value recorded for this patient, including that of his first admission in 1955. The organism, however, was apparently not yet eradicated but only in hiding. Therapy was discontinued on Jan. 31, 1957. Temperature elevation appeared on Feb. 18, and this was quickly followed by progressive lethargy and slight nuchal rigidity. On Feb. 24, amphotericin therapy was restarted, and within three days these signs had vanished. On March 9 the drug supply was interrupted, and on March 10 the patient was febrile again. Use of the drug was resumed, now in suspension form intravenously, on March 14, and that day his temperature returned to normal. Treatment was then continued, with infusions of 90 to 100 mg. every second day and with only brief interruptions, until July 25, when a water-soluble preparation of amphotericin B became available, and this

* Suggested, in response to our inquiry, by Dr. Gavin Hildick-Smith, of the Squibb Institute for Medical Research, and provided by E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation.

was substituted in a dosage of 50 mg. every second day. The last dose of the drug was given on Aug. 29, 1957.

Nuchal rigidity recurred periodically while the drug was being given in suspension form, but this symptom did not recur after July, 1957. Some spiking fever, coincident with or immediately subsequent to infusion of the drug, occurred during the month of August, but each episode lasted for only a few hours.

Post-treatment lumbar punctures were done on Sept. 19, Nov. 20, Jan. 21, and March 25, the last being about seven months after treatment was stopped. No fungal elements have been seen. The lowest sugar level, that of Nov. 20, was 62 mg. %. Cell count has varied between 0 and 1. All cultures, including that of March 25, were reported negative after one month's incubation. Spinal fluid manometric studies, which had indicated incomplete but marked subarachnoid block for many months, were essentially normal on March 25. The patient, however, was left with severe dementia and flaccid paraparesis.

CASE 2.—A 34-year-old man with a nine-year history of recurrent generalized lymph node enlargement was first admitted to the V. A. Research Hospital in May, 1956. He complained of midback pain and rapidly developed partial paraplegia. Thoracic laminectomy was done, and an extradural tumor partially removed. Histologic diagnosis was Hodgkin's disease. He received x-ray therapy over the lesion and was discharged free of neurologic signs. He reentered in November, 1956, complaining of fatigue, and developed symptoms of respiratory infection. The latter responded to penicillin, and he was discharged improved.

The patient reentered in February, 1957, for reevaluation of the Hodgkin's disease and follow-up of left lower lung field nodular densities. The latter were improved on x-ray films, but while hospitalized the patient developed frontal headache. Neurological examination was normal, as were an electroencephalogram and films of the skull and paranasal sinuses. Lumbar puncture yielded normal-appearing fluid with sugar of 39 mg. % and cell count of 21. Culture yielded encapsulated yeast organisms which were subsequently identified as C. neoformans.

Amphotericin B suspension was started intravenously on April 10. The oral form was subsequently substituted, but by the end of May, in spite of a daily dose of 4.8 gm., headache was increasing in severity and nuchal rigidity appeared. Lumbar puncture on June 3 yielded viable yeast organisms. Sugar was 23 mg. %, cell count was 50, and pressure was markedly increased. The suspension was again given intravenously, now in larger doses, varying from 80 to 100 mg. every two days. Sugar rose to 31 mg. %, and pressure approached normal. Treatment was supplemented with intrathecal injections of 0.5 to 0.8 mg. of aqueous solution. When the aqueous form became plentiful in July, the drug was given intravenously, 50 mg. every two days, and intrathecal injections were discontinued. Treatment was stopped on Aug. 4 because of a change in the patient's condition characterized by weakness, nausea, and ileus and accompanied by abnormal liver-function tests and severe serum potassium deficiency, with associated ECG changes. This syndrome was attributed by the medical consultant to viral hepatitis and responded well to parenteral potassium administration. The patient was released from the hospital, essentially asymptomatic except for fatigability, about five weeks after onset of this acute condition. No further amphotericin therapy was given. He was seen on Oct. 16 and Nov. 19, 1957, and on Jan. 15 and March 27, 1958. On these occasions he was essentially symptom-free, and neurologic examination was negative. On the latter two dates, five and seven and one-half months after amphotericin treatment was stopped, he was back at work as a factory inspector.

The last positive spinal fluid culture was obtained on the specimen of June 18, 1957, about two months after therapy was started. Disintegrating capsules were found as late as July 2, but none were seen thereafter. The most recent spinal fluid examination, on March 27, 1958, revealed no yeast elements on smear or culture, cell count 0, and sugar 55 mg. % (blood sugar was 90 mg. %).

Comment

Appelbaum and Shtokalko have reported a case of Cryptococcus meningitis in which treatment with amphotericin B was begun about 2½ months after the onset of symptoms and continued for about 12 weeks.[9] The patient was discharged essentially symptom-free three and one-half months after treatment was started, and was found so on follow-up seven months after discharge. The last post-treatment lumbar puncture, done three weeks after the drug was stopped, revealed spinal fluid findings to be essentially normal, except for a cell count of 30.

Rubin, Lehan, and Furcolow employed amphotericin B for a patient critically ill with acute pulmonary histoplasmosis.[10] To these authors "the prompt fall in temperature, the clinical response and the rapid

resolution of pulmonary infiltrates coincident with the institution of intravenous therapy suggests the possibility of some therapeutic effect." They called attention, however, to the inherently good prognosis in this condition even in the absence of specific therapy.

In both of these cases significant improvement was not obtained until intravenous administration of amphotericin B was substituted for use of the oral form of the drug. Experience in our second case was similar. In our first case there was striking improvement with oral therapy but strong evidence of smoldering infection until the intravenous therapy was used.

Good fungistatic effect in vitro against Histoplasma capsulatum as well as C. neoformans has been demonstrated for amphotericin B by Louria et al.[11] In the same report, in vivo activity against H. capsulatum infections in mice was shown.

Amphotericin B ointment has been found effective against cutaneous candidiasis in children.[12] Potency was of the same order as that of nystatin. It is probably worth while to note here that Applebaum had tried nystatin in two cases of Cryptococcus meningitis and found it ineffective.[9]

We did not find the drug unduly toxic. Large oral doses were tolerated without gastrointestinal symptoms. Intravenous injection of the suspension form was attended by troublesome pyrogenic reaction, which was less when the water-soluble form was given. Intrathecal injection produced a similar pyrogenic response. BUN was elevated as high as 25.6 mg. % during treatment of the first case described but remained normal in the second. We do not believe there was any causal relationship between the drug and the acute illness which occasioned its withdrawal in the second case.

We did not observe the effects of exclusively intrathecal therapy over any significant period of time. Several assays of spinal fluid drug concentrations were made after intrathecal injections. Four days after injection no detectable level was found. Assay 24 hours after injection of 0.6 mg. revealed 0.6μg. per milliliter. On two occasions, assay 48 hours after injection of 0.76 mg. revealed 0.6μg. and 1.5μg. per milliliter, respectively, both within the in vitro fungistatic range.

Summary

Two cases of cryptococcal meningoencephalitis have been successfully treated with a new antibiotic. One 34-year-old man with a one-and-one-half-year history of central nervous system cryptococcosis was at the point of death in spite of five weeks of treatment with cycloheximide (Actidione). Treatment with a new antifungal agent, amphotericin B, produced remarkable clinical improvement. When the drug was withdrawn after six months of oral therapy, evidence of recurrence of infection was observed. Seven months after a second six-month course of treatment by the intravenous route was concluded, there is no evidence of recurrence. A second 34-year-old man, with a 10-year history of Hodgkin's disease, developed symptoms of central nervous system cryptococcosis. Oral amphotericin B therapy was started six weeks after onset of symptoms, but after seven weeks of treatment symptoms and laboratory data indicated progression. Two months of intravenous administration produced complete remission, which persisted at the last examination, seven and one-half months after treatment was stopped.

Spinal fluid cultures, drawn seven months and seven and one-half months, respectively, after treatment was stopped, were sterile after one month's incubation, and spinal fluid sugar and cell count were normal at these times.

At this date we have confirmed arrest in two cases. Longer follow-up periods will be necessary to establish cures. We can recommend, however, the continued use of this drug in an otherwise fatal disease.

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Ruptured Aneurysm of the Circle of Willis Associated with Polycystic Kidneys

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"Berry" aneurysms of the circle of Willis and polycystic disease of the kidneys are presumed to be the result of congenital developmental defects. Both occur relatively infrequently. Their simultaneous occurrence in the same patient is more or less of a medical curiosity. Suter [1] reported 27 congenital aneurysms of the basal cerebral arteries in 5960 consecutive autopsies. In this group of 27, polycystic kidneys were found in 2. Bigelow [2] reviewed the entire problem in an excellent contribution in 1953. He collected 32 proved examples of the combination of intracranial aneurysm and polycystic kidneys from the literature. He added three cases from his own autopsy experience.

Report of a Case

A 42-year-old single woman employed as a clerk had always been in good health, except for recurring migraine headaches, until five weeks before she came under our observation. At that time she had the sudden onset of headache, nausea, and vomiting. She was ill for four days, and then she seemingly recovered and returned to work. She remained symptom-free until five weeks later, when she suddenly complained of severe headache once more. She began to vomit and within a matter of 15 or 20 minutes she collapsed and was taken to a hospital. Examination showed nuchal rigidity and positive Babinski signs on both sides. On abdominal palpation a firm movable mass about 6×10 cm. was found in the right upper quadrant. Her blood pressure was 134/84. The patient's general condition improved, and seven days later an abdominal exploration was done. The kidneys were both found to be enlarged and cystic, the right one more than the left. The patient's condition seemed satisfactory; she did, however, complain of headache. This became more and more severe. On the second postoperative day, nuchal rigidity was noted once more and the patient was somewhat confused. A spinal puncture done at this time disclosed a xanthochromic cerebrospinal fluid. The next day the patient lapsed into stupor. A second spinal puncture was done. The cerebrospinal fluid was now grossly bloody. Following this, there was marked improve-

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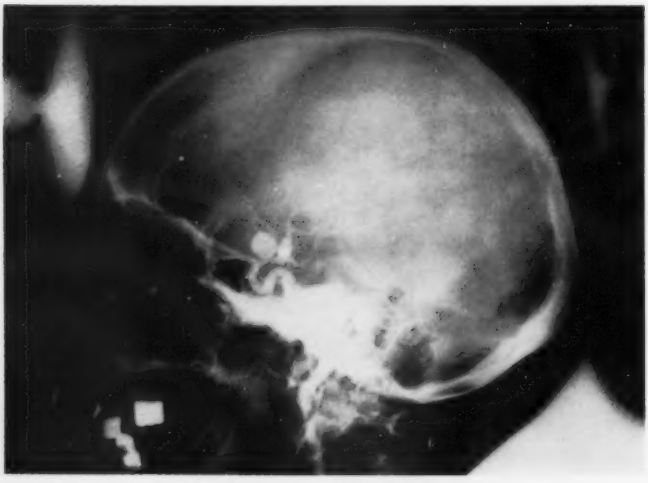


Fig. 1.—Result of right carotid angiography, showing aneurysm of internal carotid artery. Lateral view.

Fig. 2.—Frontal projection of right carotid angiography.

ment in the state of consciousness. The patient's general condition became progressively better, and 22 days after her ictus she was transferred to our care. At this time she was lethargic but easily rousable. Nuchal rigidity was present, as were bilateral Babinski signs. There was a marked droop of the right upper eyelid. Spinal puncture at this examination disclosed a xanthochromic fluid under a pressure of 260 mm. The electroencephalogram showed a profound slow abnormality diffusely distributed. On bed rest and symptomatic treatment she improved rapidly.

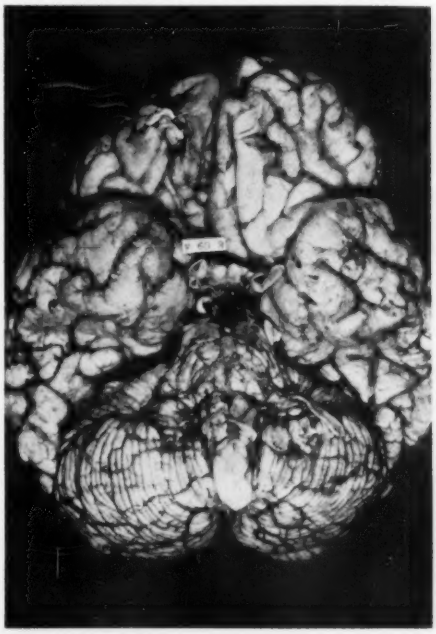
Nine weeks after the onset of the subarachnoid hemorrhage, the right common carotid artery was exposed with the use of local anesthesia. An angiogram, done with 35% iodopyracet (Diodrast), disclosed an aneurysm of the internal carotid artery about 1 cm. in diameter and about 1 cm. proximal to the bifurcation of the carotid artery into the anterior and middle cerebral arteries (Figs. 1 and 2). As soon as the x-ray films were interpreted, the common carotid artery in the neck was doubly ligated and divided between the ligatures. The patient had an uneventful course and was discharged to her home two weeks later. Within four or five months she returned to her regular employment.

During the next few years there were no major symptoms. She no longer complained of migraine headaches, which were present prior to the subarachnoid hemorrhage. Her blood pressure was around 150 systolic and 100 diastolic on most examinations. About four years after the subarachnoid hemorrhage she noted night cramps in both calves as well as morning nausea and vomiting. Within two or three weeks she complained of pruritis, weakness, and dysuria. Uremia was suspected, and she was hospitalized. Laboratory examination of the urine and blood confirmed the clinical diagnosis. The cerebrospinal fluid was normal in every respect. In spite of vigorous treatment, the patient became comatose after four days in the hospital, and she died 4 years and 10 months after the subarachnoid hemorrhage.

Autopsy.—An autopsy was performed by Dr. Papadikes, who furnished us with a protocol and permitted us to study the brain. The positive findings were as follows. There was a healed scar on the right side of the neck, beneath which the right common carotid artery was ligated about 1 cm. above the bifurcation of the innominate artery. The lungs were congested and edematous. The aorta showed slight arteriosclerosis, particularly in the abdominal aorta. The right kidney weighed 910 gm.; the left, 860 gm. Numerous fluid-filled cysts of varying sizes were found in both kidneys. No functioning renal tissue was apparent on gross inspection.

Neuropathologic study was done by Dr. Feigin. The brain weighed 1200 gm. The cerebral hemi-

Fig. 3.—Asymmetry of cerebral hemispheres due to decrease in size of right frontal lobe.



spheres were asymmetric, owing to a decrease in the size of the right frontal lobe (Fig. 3). The right orbital gyri were shrunken and retracted. Elsewhere the gyri were normal, as were the brain stem and cerebellum. An unruptured aneurysm was present on the right internal carotid artery (Figs. 4 and 5). It measured 7 mm. in diameter. The other vessels at the base were normal.

On section, a cystic lesion 7×3.5×3 cm. was found in the right frontal lobe. It was lined by an irregular, gray, lacy membrane. The cavity communicated with the frontal horn of the right lateral ventricle. The ependymal surfaces of the right lateral ventricle showed a coarse irregular granularity. This was evident in the third as well as in the fourth ventricle. On section, the cerebellum and brain stem were normal.

Microscopic examination of the wall of the aneurysm showed it to be made up of a densely hyalinized collagenous membrane. The lumen was patent. The adventitia contained moderate numbers of large mononuclear cells and a few lymphocytes. The wall of the old hemorrhagic cyst of the right frontal lobe was composed of a condensation of glial fibers intermingled with many hypertrophied astrocytes. There were numerous phagocytic cells, some containing brown granular pigment. In the region of the right caudate the ependymal lining was discontinuous. The tissues under the ependyma were rarefied in this zone, and a prominent astrocytosis was present.

Fig. 5.—Reconstructed circle of Willis.

Fig. 4.—Aneurysm of right internal carotid artery. Photograph made after lesion was cut across at autopsy.

Comment

Bigelow [2] has called attention to the relationship of congenital intracranial aneurysms to other developmental defects. Coarctation of the aorta, a relatively rare congenital malformation, has been found often enough in association with intracranial aneurysms so that the potential relationship of these two disorders is now well recognized. Likewise, cases of the association of intracranial aneurysm and polycystic kidneys have now been reported in sufficient numbers that there appears to be more than just an incidental relationship. A compilation of available statistics by Bigelow disclosed 21 examples of polycystic kidneys in a group of 360 cases of congenital intracranial aneurysms, an incidence of 5.9%.

Our case is of interest not only because two rare congenital anomalies in the same

patient were discovered during life but also because it is one of the few cases where an autopsy was done several years after ligation of the common carotid artery for a ruptured aneurysm of the circle of Willis. It is of some interest that after ligation of the common carotid artery the patient never had migraine headaches, which had been very troublesome prior to the subarachnoid hemorrhage. This is by no means a unique observation. It has been reported many times previously. In this patient, ligation of the carotid artery in the neck appears to have protected her from further bleeding from the aneurysm. This statement requires qualification, since many persons who recovered from an attack of subarachnoid hemorrhage due to the rupture of an intracranial aneurysm never bleed again, even though carotid ligation or other surgical measures are not done. In our case, although the aneurysm found at autopsy did not appear to be very much smaller than it was during life, as demonstrated in the angiogram, the wall of the aneurysm was made up of a dense hyalinized collagenous membrane with no apparent thinned-out or weak areas. The lumen of the aneurysm was patent, and there was no clot in the aneurysm. It is generally accepted, and there is some experimental proof, that the ligation of the common carotid artery in the neck, or the internal carotid artery in the neck, significantly reduces the systolic pressure in the intracranial portion of the internal carotid artery. The rationale of ligation of the carotid vessels in the neck for the treatment of intracranial aneurysms is based on this hypothesis. Mount and Taveras[3] performed progress arteriography in a series of 37 patients with intracranial aneurysms. In 28 the internal carotid artery had been ligated. In the remaining nine the common carotid artery had been ligated. In 10 patients who had an aneurysm of the internal carotid artery and where ligation of the internal carotid artery was done, the aneurysm was no longer visualized in 8. In two it was the same size as prior to ligation. In four patients who had an aneurysm of the middle cerebral artery and who had complete ligation of the internal carotid artery, the aneurysm was no longer demonstrated in one and in the remaining three it was smaller. In 16 patients who did not have surgical therapy, progress arteriography showed the aneurysm to be the same size or larger. Only tentative conclusions are possible from such a small series. Nevertheless, it would appear that ligation of the internal carotid artery in the neck or the common carotid artery in the neck has a definite place in the treatment of aneurysms of the circle of Willis.

The finding of an old hemorrhage of the right frontal lobe communicating with the right lateral ventricle was not entirely unexpected. Such lesions, in association with rupture of an intracranial aneurysm, are frequently demonstrated by arteriography during life. They often play an important part in the clinical course and in the method of treatment.

In an analysis of 93 autopsy records, Robertson[4] found congenital aneurysms in 86 patients. In 51 a massive hemorrhage into the brain was found. Robertson pointed out that the most important factor in the development of an intracerebral rupture is the location of the aneurysm. Aneurysms of those arteries which are free on the base of the brain tend to rupture into the subarachnoid space, while those which lie between cerebral surfaces are more likely to rupture into the brain.

Summary

A case of a ruptured congenital intracranial aneurysm of the internal carotid artery associated with bilateral polycystic kidneys is described. Rupture of the aneurysm into the subarachnoid space and right frontal lobe resulted in alteration in cerebral function and meningeal irritation, for which the patient was hospitalized. After the demonstration of an aneurysm of the

internal carotid artery, the common carotid artery was doubly ligated and divided. Recovery took place and the patient remained symptom-free for 4 years and 10 months and worked at her previous position. Signs of uremia developed and death occurred 58 months after the subarachnoid bleeding. The autopsy findings are reported.

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Anxiety as a Manifestation of Pheochromocytoma

Report of Two Cases

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The situation (modern professionalism) is dangerous. It produces minds in a groove. Each profession makes progress but it is progress in its own groove . . . the groove prevents straying across country . . . there is no groove of abstraction which is adequate for comprehension of human life.

A. N. Whitehead

Pheochromocytomas simulating acute anxiety attacks [1] and the hypermetabolic state [2] have been reported. In fact, the features of this tumor are so well known it has prompted Kvale [3] to remark that definite clues can be obtained as to the presence of this tumor at the first or second office visit. Watkins [2] reaffirms that our knowledge of these tumors is "sufficient to permit a diagnosis by the thoughtful physician in nearly all cases."

The purpose of this paper is to present two cases where long-standing anxiety seemed to predominate and to emphasize the similarity between this syndrome and chronically discharging pheochromocytoma. In each case the confusion of etiologies led to considerable difficulty in diagnosis.

Report of Cases

CASE 1.—A 21-year-old white man was admitted to the Akron General Hospital on Jan. 22, 1957.

Chief Complaint.—Severe apprehension, heart pounding, and substernal pain of a few hours' duration.

Present Illness.—In December, 1955, the patient visited his physician with complaints of vague lower abdominal pains and constipation of several months' duration. A barium enema and an upper gastrointestinal series were done and reported as normal. In March, 1956, the patient was referred to an internist. A history disclosed that two years before his mother was found to have carcinoma of the cervix and died within a few months. Since that time the patient had become tense, nervous, and easily upset, with some palpitations. The constipation now required medication and enemas. He lost 5 lb. and was unable to work regularly. A physical examination in March, 1956, revealed a blood pressure 132/120 in the left arm and 134/110 in the right. The pulse rate ranged from 92 to 120 per minute. Weight was 140 lb. He was described as well muscled but thin. Cold clammy extremities were noted. Laboratory studies produced normal blood cell counts and a trace of albumin, with a few granular casts in the urine. A. B. M. R. was —2 and a two-hour p. c. sugar test was 85 mg. %. He was referred to his local physician again with the diagnosis of emotional lability in a tense asthenic young man with an irritable colon. The persistence of these symptoms prompted the patient to go to a third physician about six months before ultimate hospitalization. He was treated symptomatically, but on the day of admission he complained of apprehension, heart-pounding, and substernal distress of a few hours' duration. Blood pressure was "over 200," and he was immediately hospitalized for an ECG and evaluation for a pheochromocytoma.

Physical Examination.—Blood pressure, 200/130 mm. Hg; temperature, 99 F; pulse rate, 120 per minute; respirations, 20 per minute; weight, 140 lb.

Laboratory Examination.—Blood cell counts were normal. Urine showed a trace of albumin, no sugar, and normal sediment. ECG's were normal.

Roentgenographic Examination.—Chest films were normal. Intravenous urographic examinations showed a mass in the superior pole of the right kidney. This was confirmed on retroperitoneal air studies (Fig. 1).

Hospital Course.—Phentolamine (Regitine), 5 mg., was injected intravenously, and within two minutes the blood pressure fell from 200/130 to 110/70. This was repeated several times. A confirmatory piperoxan antidiuretic test was performed according to the method of Corcoran [4] (Fig. 2). The 10-minute urine volumes fell markedly after 20 mg. of piperoxan.

Operative Findings.—A 110 gm. adrenal tumor was removed on Feb. 4, 1957, measuring 9 cm. in greatest diameter. It appeared mottled, yellowish tan in color, and soft and spongy in consistency. The parenchyma was infiltrated with streaks of blood.

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Fig. 1 (Case 1).—Retroperitoneal air study performed Jan. 25, 1947, showing a mass in the superior pole of the right kidney.

Phentolamine, 25 mg. was given over a two-hour period during surgery to maintain a normotensive state.

Histopathology.—Large polyhedral cells with finely granular cytoplasm were seen on microscopic section (Fig. 3A).

Follow-Up.—One year later the patient had gained 30 lb. and the blood pressure has been consistently recorded at 120/80 mm. Hg. He works regularly, and the constipation and anxiety have disappeared. The urine cleared spontaneously.

CASE 2.—A 39-year-old white man was admitted to St. Thomas Hospital on April 11, 1957.

Chief Complaint.—Nervousness, weakness, weight loss, anorexia, and diarrhea.

Present Illness.—About 15 years previously the patient, a piano teacher, unmarried, had been accused by one of his pupils of sexual advances. He was tried and acquitted, but the resultant "emotional trauma" left him extremely "nervous." His weight was around 130 lb. Four years before hospitalization he had an onset of diarrhea, characterized by three to four loose watery brown stools a day. He suffered from mild lower abdominal cramping but noted no mucus or blood. Two physicians were seen for these complaints. One told him his blood pressure was elevated, and both said he was obviously nervous from his courtroom experiences. Later, and against his wishes,

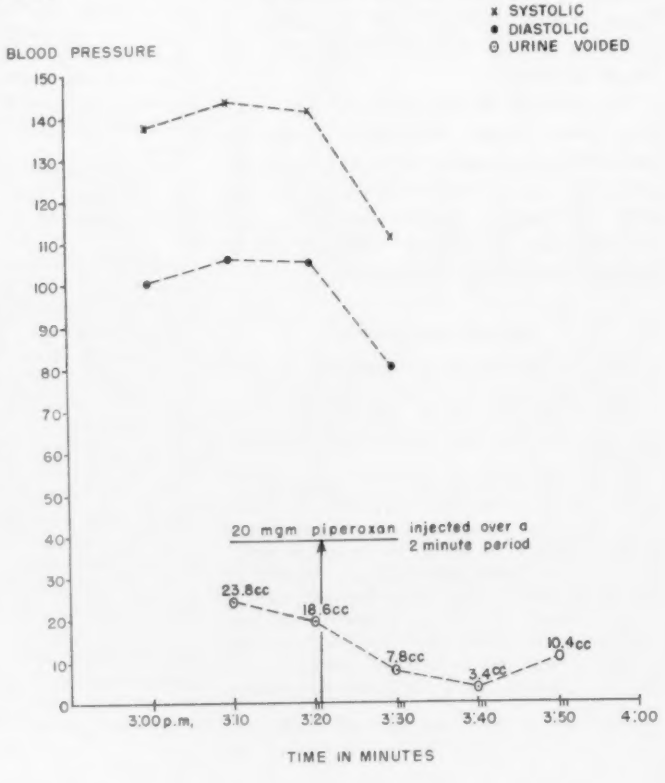

Fig. 2.—Phentolamine antidiuretic test. Note the baseline 10-minute urine volume average of 21 cc. After 20 mg. of intravenous phentolamine this volume fell to an average of 7 cc.

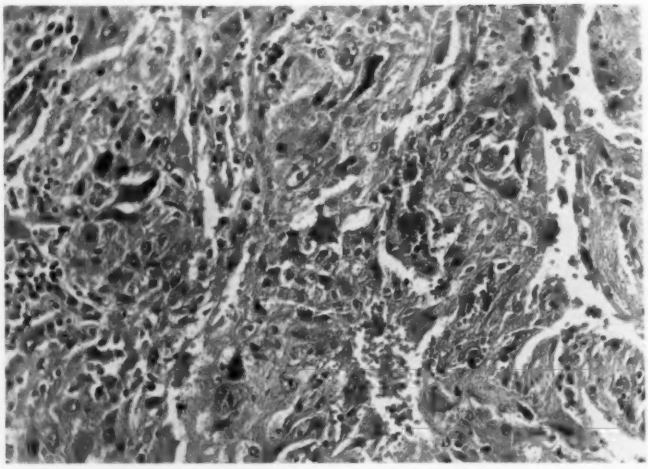

Fig. 3A (Case 1).—Microscopic section, showing characteristic large polyhedral cells with finely granular cytoplasm.

he was persuaded by his family to visit a third physician. Loss of appetite and 25 lb. of weight and a restricted existence characterized the patient prior to the examinations.

Physical Examination.—Blood pressure, 120/82 mm. Hg; temperature, 98 F; pulse rate, 110 per minute and regular; weight, 105 lb. He was tremulous, apprehensive, and thin and had clammy palms. The remaining examination, including proctoscopic, was unremarkable.

Laboratory Examination.—Blood cell counts were normal. Urinalysis showed a specific gravity of 1.003; albumin, 3+; no glycosuria, and sediment with numerous white cells and with a few cellular and hyaline casts. The initial impression was chronic nephritis and colitis, type unknown. Hyperthyroidism was to be ruled out.

Roentgenographic Examinations.—X-rays of the colon revealed a soft-tissue mass obscuring the right kidney. A subsequent intravenous pyelogram showed the mass to be arising from the superior pole of the right kidney, and a pheochromocytoma was suspected. B. M. R. was +2, and PBI was normal. Unfortunately, diagnostic tests for this tumor were not performed.

Operative Findings.—At surgery, on April 12, 1957, the blood pressure rose to 188/90 at the end of the first hour but gradually returned to normal without specific therapy. A 10×9×7.5 cm. adrenal tumor was removed. It was yellowish brown and had a cystic somewhat hemorrhagic center. Microscopic sections showed large irregular cells containing cytoplasmic granules (Fig. 3B). One of the many sections showed capsular invasion in small

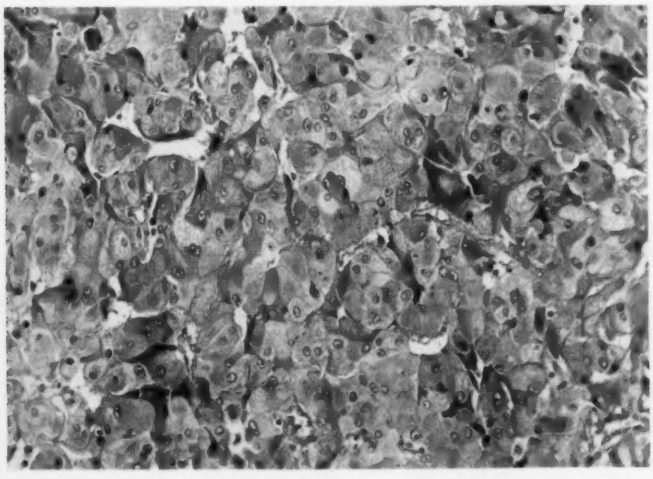

Fig. 3B (Case 2).—Microscopic section, showing cells similar to Figure 3A.

areas. Because of this a diagnosis of malignant pheochromocytoma was made.

Follow-Up.—Nine hours after surgery the blood pressure fell to 90/50, but it rose to 110/70 after 25 mg. of ephedrine sulfate was given intramuscularly. Ten months later, appetite has returned and weight has risen from 105 to 153 lb., with a blood pressure in the range of 140/90. Although he still feels somewhat anxious, his general well-being has improved tremendously, he is more outgoing, and the diarrhea has ceased. Of interest is the development of asthma of unknown etiology during the fall months. Urinalysis has returned to normal without treatment.

Comment

Anxiety is defined as having both subjective and objective components. Subjective components of fear, panic, apprehension, bowel complaints, and precordial pain have been reported. Physical findings of tachycardia, tachypnea, clammy skin, tremor, hypertension, and weight loss are known. Masserman[5] states, "It may be free floating in type and every shade of intensity from mild uneasiness to panic can occur and the nature of the anxiety differs greatly with the changing contingencies of stress and resolution of conflict." His differential diagnosis of anxiety includes hyperthyroidism, cardiac disease, hypoglycemia, certain neurologic disorders, Addison's disease, and hysterical tetany. However, he feels "true anxiety" is characterized by unmistakable feelings of subjective apprehension and conflict.

Following Cannon's[6] work, Starr,[7] in 1937, reported detailed measurements of pulse rates, blood pressures, metabolic rates, arteriovenous oxygen differences, respiratory rates and volumes, and peripheral circulatory resistance in human subjects following injections of epinephrine and ephedrine. The subjective symptoms were ignored.

In 1950 Goldenberg[8] did somewhat similar studies with epinephrine and levarterenol (*l*-norepinephrine) injections in human subjects. The subjective sensations were classed as 1+ with epinephrine, and those with levarterenol ranged from *no* change to 1+. Goodman and Gilman[9] further isolated these symptoms as restlessness, apprehension, headaches, precordial pain, and tremor in certain persons. Increases in systolic blood pressure and increases in respiratory rate and volume were noted with both drugs. The cutaneous blood flow decreased with both but more consistently with epinephrine.

It is obvious from the foregoing that there are certain similarities between anxiety states and those from injections of epinephrine and levarterenol.

In Case 1 the recent death of the patient's mother was believed to play an important part in the production of the anxiety. Although anorexia, clammy skin, constipation, and hypertension are reported effects of hyperadrenalism, they only served to strengthen the initial impression of functional disease. Of interest is the baseline blood pressure of 140/90 mm. Hg recorded in the hospital between attacks (Fig. 2). Following 5 mg. of intravenous phentolamine this fell to 90/70. This suggests that the tumor was chronically discharging between paroxysms of hypertension. Following removal of the tumor both subjective and objective findings of anxiety improved markedly.

In Case 2 the anxiety was again attributed to psychic factors. An unjust accusation with resultant trial and acquittal was an important "cause" of weight loss, diarrhea, apprehension, and a restricted life. Only during surgery was an abnormally high blood pressure recorded, of 188/90 mm. Hg. Again, following removal of the tumor, the anxiety greatly improved. The patient has gained 45 lb.; the tension is reduced, and the diarrhea has ceased.

It is difficult to see how a more detailed psychiatric history could have led to an earlier solution of these two problems; an awareness of the similarities of anxiety syndromes and epinephrine and levarterenol discharge might have.

Summary

Two cases are reported of pheochromocytomas where psychic factors were believed to be the cause of restricted lives, anorexia, weight loss, gastrointestinal symptoms, and clammy skins. An episode of marked hypertension led to the diagnosis in one case but was never a prominent feature of the other. The second was found during barium enema and intravenous pyelogram examinations. The report emphasizes the similiarity of the anxiety syndrome and chronically discharging pheochromocytoma.

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The Isolation of Adenovirus Type 1 from a Fatal Case of Viral "Pneumonitis"

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The etiology of acute respiratory infections of childhood and infancy often remains obscure. Progress has been made, however, in the classification of these illnesses by the recent discovery of a new group of viruses, subdivided into distinct serotypes, which are now referred to as adenoviruses,[1] formerly the APC,[2] RI,[3] or ARD[4] groups. Adenoviruses have been shown to be a cause of undifferentiated acute respiratory disease, nonstreptococcal exudative pharyngitis, and primary atypical pneumonia. They were also found to be associated with a clinical entity designated pharyngoconjunctival fever, which may assume epidemic proportions.[3-8] Other illnesses have been ascribed to these agents which include epidemic keratoconjunctivitis[9,10] and mesenteric lymphadenitis,[11] and a Type 3 of these agents has been isolated from a stool of an infant with a disease resembling roseola infantum.[12] While in general the diseases induced appear to be relatively mild, adenoviruses have been isolated from the lungs of two fatal cases of pneumonitis,[10] and a third case has been reported from Japan.[11]

The present report concerns the isolation of adenovirus Type 1 from the lung of a fatal case of viral "pneumonitis" in a 14-month-old child.

Report of Case

Clinical History.—The patient, a 14-month-old white girl, had enjoyed good health until April 20, 1955, when she developed a mild upper respiratory infection. On the evening of the sixth day after onset the child became slightly drowzy. The next morning she did not look good and refused food. In the afternoon tonic-clonic convulsions began. The temperature was 103 F. There was marked generalized rigidity but no focal neurological signs. From this time until her death, on April 30, 1955, the child remained unconscious. Convulsions occurred at almost hourly intervals, each lasting up to 30 minutes.

The patient was brought to Bryn Mawr Hospital on the evening of April 27, 1955. Physical examination revealed an acutely ill child in severe respiratory distress. Temperature: 103 F. B. P.: 95/45. Pulse: 140 per minute. The pharynx was injected and filled with pink mucus. Direct laryngoscopy revealed swollen membranes with mucoid discharge. There was slight enlargement of the nodes of the anterior cervical chain. Auscultation of the chest revealed diminished breath sounds and wheezes throughout both lung fields. Moderate abdominal distention was present. Reflexes could not be adequately elicited because of generalized rigidity. There were no meningeal signs. Injection of both ear drums with bulging on the left was noted. Incision yielded a small amount of serous material, which was cultured.

Laboratory Data.—Hemoglobin: 11 gm. %; WBC, 12,800, with 73% polymorphonuclear cells.

Urine: 3+ glucosuria; negative for protein, acetone, diacetic acid, and formed elements; negative for salicylates.

Serum Calcium: 6.0 mEq. per liter. Chlorides: 80 mEq. per liter. CO_2: 41 vol. %.

Spinal Fluid: chloride, 592 mg. %; protein, 20 mg. %; sugar, 135 mg. %; 3 red cells per cubic millimeter; no WBC's; no growth on culture.

Hospital Course.—Immediately following examination the child experienced another convulsion, and these continued until the time of death. For a time during the first hospital day, they tended to become focal, involving the left side of the body, but later they again became generalized and continued so. On the second hospital day increasing respiratory difficulty was noted. Copious amounts of pinkish mucoid secretions had to be aspirated

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frequently. Because of continued severe seizures, an infusion of 0.25% thiopental (Pentothal) sodium was started on the morning of the second hospital day. An hour after the infusion was discontinued, respiratory arrest developed. The child was then removed to a respirator, where she remained until her death on the evening of April 30, 1955. Terminally, the temperature fell to subnormal levels and the pulse showed marked variation (20 per minute to 190 per minute). A second lumbar tap, on April 28, 1955, yielded clear fluid which contained 102 RBC per cubic millimeter and no WBC's.

Pathology

Macroscopic Examination.—Pleural Cavities: On the right there is about 120 cm. of clear amber fluid, with a large protein coagulum. No fluid was recovered on the left.

Lungs: The right lung weighs 125 gm; the left, 100 gm. All lobes, except the anterior portion of the left upper one, show dark purplish discoloration and have a doughy diffuse rubbery consistency. The bronchi contain large amounts of tenacious opaque pink-brown mucoid secretion.

Spleen: Weight 55 gm. Moderately congested with numerous large follicles.

Lymph Nodes: Diffuse prominence of lymph nodes, especially in the small bowel, mesentery, and mediastinum.

Ears: Opening of the middle ears reveals a thick serous fluid in the right.

Brain: Removal of the calvarium shows the brain to be under markedly increased pressure, with flattening of the gyri and narrowing of sulci. There is diffuse softening. No evidence of meningeal opacities.

All other organs essentially normal.

Microscopic Examination.—Lungs: Extensive pneumonia. Massive intra-alveolar and some interstitial infiltration with fibrin, polymorphonuclear and small round cells, and, in some areas, macrophages. Spotty necrosis of the mucous membranes of the bronchi which are filled with mucoid exudate containing polymorphonuclear and small round cells. No evidence of bacterial organisms. Enlarged intrapulmonary lymph follicles. Occasional venous organizing thrombi are noted.

Spleen: Scattered follicles with small germinal centers and normal red pulp.

Lymph Nodes: Normal.

Brain: Extensive edema of all portions. The neurons, especially in the cornua ammonis and olivary nucleus, show evidence of degeneration. No evidence of meningitis, perivascular infiltration, or encephalomalacia.

All other organs essentially normal.

Bacteriological Examination.—Premortem: Left middle ear, stool, and urine: hemolytic Staphylococcus albus (coagulase-negative). Cerebrospinal fluid (two times) and blood: negative.

Postmortem: Lung and right middle ear: Staphylococcus albus (coagulase-negative). Blood: negative.

Virus Isolation.—Specimen: Spinal fluids obtained on admission to the hospital and two days later and lung as well as brain tissues removed during the autopsy were shipped to the laboratory in the frozen state. The spinal fluids were used for inoculation without any pretreatment. The lung and brain tissues were thawed and ground with alundum in a mortar, and 10% suspensions were prepared in Hanks' balanced salt solution containing 1% horse serum. These were clarified by centrifugation at 2000 rpm for 20 minutes in a refrigerated centrifuge and then stored at —20 C. Before inoculation the suspensions were incubated at 37 C for one hour in the presence of 500 units of penicillin and 500μg. of streptomycin per milliliter.

Tissue Culture: Tissue cultures of human epithelial cells Strain HeLa[15] and of a strain of epithelial-like cells derived from normal human embryonic liver established in this laboratory[16] were employed for inoculation. The preparation of these cultures has been fully described previously.[17]

Isolation Procedure: Each of the four specimens was inoculated three times on different occasions into several tube cultures of each type of cells. The inoculum consisted of 0.2 ml. of undiluted spinal fluid or of 10%, 1%, or 0.1% organ suspension. Since the organ suspensions were slightly toxic for the tissue culture cells, the cultures were washed once with Hanks' balanced salt solution after 24 hours of incubation at 37 C and refed. Further refeedings of all cultures were performed when the media became too acid or after five and nine days of incubation.

No cytopathogenic effects were observed in all the cultures which were inoculated with the two spinal fluid specimens or with brain suspensions during 13 days of observation on first transfer or in two additional serial passages of cells and medium at 13- and 6-day intervals. In contrast, three separate sets of cultures inoculated with 10% or 1% lung suspensions showed cellular destructions after 7 to 12 days of incubation similar in appearance to those observed with adenoviruses. Transfer of cells and medium to fresh cultures yielded cytopathogenic effects in approximately 3 days, and in further serial passages, in 24 to 48 hours. Titration in HeLa cell cultures of second and further passage materials revealed infectivity titers of 10^{-3} to 10^{-5} per 0.2 ml. of inoculum. Neutralization tests (Hilleman and Werner[8]) were performed with use of 10 tissue-culture infectious

doses of the isolated virus and 1:20 dilutions of specific rabbit antisera against adenoviruses Types 1 to 6, which were supplied by Dr. R. J. Huebner, of the National Institutes of Health. In these, cytopathogenic effects were completely prevented by the antiserum against Type 1, whereas no effect was seen when the virus was mixed with antisera against Types 2 to 6, respectively. The results of the neutralization tests were confirmed by Dr. W. P. Rowe, of the National Institutes of Health. It should be mentioned that no adenovirus Type 1 was available in this laboratory prior to these studies.

Comment

In the clinical diagnosis and management of this case the possibility of a cerebral as well as of a pulmonary process had to be considered. Those of us who observed this child clinically had the impression of an acute disease of the central nervous system in the form of an encephalitis, and yet no virus was isolated from the brain or spinal fluid and the histological examination failed to reveal any evidence in this direction. The absence of confirmation of infection in the central nervous system by culture or histology emphasizes the importance of considering nonspecific as well as infectious causes of encephalopathy in patients such as this. In this patient two nonspecific causes were present: (1) anoxia secondary to the extensive involvement of the lungs and (2) hypoelectrolytemia due possibly to vomiting and to poor intake as evidenced by a serum chloride volume of 80 mEq. per liter and a spinal fluid sodium chloride of 592 mg. %. Appreciation of the possibilities of a noninfectious element playing a role in the symptomatology may at times be important in guiding therapy. The changes in the brain were compatible with the effects of anoxia and water intoxication.

Since no blood specimens from the early acute or the final stages of the case reported here were available, serological confirmation of infection with the isolated virus by demonstration of a rise in antibodies could not be obtained.

Summary

The isolation of adenovirus Type 1 from the lungs of a fatal case of viral "pneumonitis" in a 14-month-old child is reported. The clinical history and pathological, bacteriological, and virological findings are presented, and the differential diagnosis is discussed.

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CORRECTION

In the article "The Effect of Treatment on Mortality Rates in Severe Hypertension: A Comparison of Medical and Surgical Regimens," by Drs. H. Mitchell Perry Jr., and Henry A. Schroeder, the 14th, 15th, and 16th lines from the bottom of the lefthand column of page 423 repeat the statement of the preceding lines. The paragraph is complete without them.

Tomahawk Head Injury

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Many a provincial easterner of the stay-at-home variety still pictures the West and Middle-West as teeming with buffalo, stage coaches, and Indians. Recent experience with a tomahawk injury indicates that this bemused and fanciful notion is not utterly outside the realm of reality. The purpose of this paper is to report a tomahawk injury which occurred on the contemporary scene.

Report of Case

The patient, a 57-year-old merchant, was first examined on Sept. 20, 1955. He complained of headache and paralysis of both arms. He had immigrated to America at the age of 12 years; he operated a combined grocery store-filling station-trailer camp establishment. His health in the past had been excellent, except for an episode of back pain and "sciatica" in both lower extremities in 1953, treated conservatively with good results.

In early June, 1955, approximately two weeks prior to the onset of the present symptoms, the patient was summoned by neighbors to quiet a disturbance in the trailer camp. One of the residents, in an inebriated state, was administering a beating to his wife. The patient intervened, threatening to summon the police. After delivering this reprimand he proceeded to his home. His assailant gave chase, striking him in the left malar region with a tomahawk. The weapon is shown in Figure 1. The patient was rendered unconscious for a period estimated as several minutes. He was assisted to his home by friends. Medical attention at the time was not sought.

In the latter part of June, 1955, he began having pains in both temples, sharp in character, occurring several times a week during evening hours and interfering with sleep. Around the middle of August, 1955, he had an attack described as a severe pressure sensation on the top of his head. He felt faint and was obliged to lie down. He remained in bed for one week, during which time he had severe head pain. After this week long illness he was symptom-free for a period of 7 to 10 days. At the end of that time he suddenly developed severe head pain, bitemporal in location, which subsequently spread and localized to the vertex. The pain would come and go in wave-like fashion for periods of 5 to 20 minutes. During the next four weeks he continued to have irregularly occurring attacks of such head pain of gradually increasing severity and frequency. During some of these attacks he would experience numbness in the fingers of both hands, usually the right. This subjective sensation would be of transitory duration and would subside spontaneously after several minutes. On a few occasions, he had experienced, during the course of an at-

Fig. 1.—Photograph of the tomahawk (see text).

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Department of Neurology, University Hospitals.

tack, numbness of the tongue and upper lip. Several days prior to examination a severe attack had taken place, during which he found himself unable to speak for a period of 30 minutes.

At no time had he experienced difficulty with his lower extremities. His appetite and eating habits had remained normal. No weight change had been observed.

On examination, the patient was alert and cooperative and properly oriented. He spoke with a foreign accent. He was of stocky heavy-set build. The blood pressure was 140/80. Moderate nuchal rigidity was present. The external ocular examination was normal. Funduscopic examination revealed some generalized narrowing of the arterial vessels. The optic disk margins were blurred and indistinct; peripapillary edema was present bilaterally. A single perivenous splinter hemorrhage was observed overlying the left disk margin in its lower and outer aspect.

Examination of the heart, lungs, and abdomen revealed no abnormalities. The extremities were symmetrical and of normal strength. Tests of coordination were normal. Sensory examination disclosed no unusual findings, and the stretch reflexes were considered normal. The station and gait were not unusual.

Routine studies of the blood and urine were normal. Blood serologic tests for syphilis were negative. X-rays of the chest and skull were normal. The calcified pineal shadow was in normal position.

Spinal fluid examination done on the second hospital day produced clear xanthochromic fluid under an initial pressure of 300 mm. During the procedure the patient had an attack, with numbness and weakness of the left hand and forearm the presenting features. The spinal fluid contained 10 mononuclear cells per cubic millimeter, and the Pandy test was 1+. The total protein was 78 mg. %. (The closing spinal fluid pressure was 280 mm.)

The clinical impression was that of "expanding intracranial lesion, probably bilateral subdural hematomas." Neurosurgical consultation was obtained; trephination was advised. At operation bilateral subdural hematomas were evacuated through parietal trephines; 200 cc. of liquid yellow-brown material was removed, from the left side and 75 to 100 cc., from the right. The postoperative course was uneventful, and the patient was discharged on the ninth hospital day.

During the following month the patient was readmitted on two separate occasions because of continued attacks of numbness and weakness in the extremities on the left side and intermittent drainage from the right parietal trephine wound. A subgaleal abscess at the right trephine site was incised and drained on the first readmission, and on the subsequent admission craniotomy on that side was carried out, with evacuation of a large thickly encapsulated subdural abscess. Following this last procedure his course was characterized by progressive improvement, and he was discharged to his home on Nov. 17, 1955.

The patient was admitted to University Hospitals for a fourth time on July 2, 1956, complaining of pain in the medial aspect of the right leg and foot. On examination the striking findings were moderately severe weakness of the right quadriceps group, together with some weakness of the hamstrings and ankle dorsiflexors on that side. Subjective hyperesthesia over the right leg anteriorly and distal right thigh was reported. The quadriceps reflex on the right was absent.

Hemilaminectomy was carried out three days later, and protruding degenerated intervertebral disks were removed at the L3-4 and L4-5 levels. The patient's subsequent course was characterized by gradual improvement. He has since returned to work and is free of symptoms.

Comment

Trephination as practiced among primitive peoples has been a subject of intense interest for many investigators.[1-5] Archaeologic findings indicate the origin of the procedure during the early Neolithic pe-

Fig. 2.—Peruvian skull showing trepanation. Reproduced through the courtesy of Major.[6]

Fig. 3.—Prehistoric adult male American Indian skull, showing left posterior frontal defects presumed to be traumatic in origin. Excavated near La Crosse, Wis., in 1940. Reproduced through courtesy of the Milwaukee Public Museum.

riod *—some 10,000 or more years ago.[5,6] Major [6] has stated, "During the Neolithic or New Stone Age, man practiced the operation of trepanning, employing a flint knife for this purpose" (Fig. 2).

More apropos to the case at hand are the causes of head injury leading to the procedures of trephination or craniotomy. Explorations in Peru have shown that many of such head injuries were caused by a macana, a wooden weapon edged with sharp flint. Specimens examined revealed that most of the fractures and craniotomy defects were on the left side; the investigators concluded that the majority of blows had fallen on that side from right-handed adversaries.[1] Statistics as to the incidence of head injury due to tomahawk blows among American Indian peoples are not available. Figure 3 shows a defect in an American Indian skull presumed to be of traumatic origin.

If this patient had not had the benefit of modern surgical therapy, it is very likely that he would have died and been buried in some contemporary Iowa cemetery. As it is, sometime in the distant future, an archeologist may come across a trephined and craniectomized skull in an Iowa burial site and speculate upon the anachronism of tomahawk injuries in the 20th century.

* Studies show the beginning of the Neolithic period to be around 20,000 B. C. in Persia, 15,000 B. C. in the Mediterranean region, and 10,000-11,000 B. C. in western Europe. There are today, in parts of New Guinea, Stone Age cultures; so, strictly speaking, the period still is in existence.

Summary and Conclusion

A craniocerebral injury induced by an ancient Indian tomahawk is reported. This led to a series of unhappy sequels from which the patient eventually made good recovery. Man's inhumanity to man thus finds curious reactions, and history repeats itself.

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Treatment in Internal Medicine

Treatment of Tetanus

Therapy of Tetanus from 1905 to 1956, Gorgas Hospital

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Tetanus is not a commonly encountered disease; consequently, individual physicians acquire little experience with this grave medical emergency which requires prompt and expertly administered treatment. Since medical literature on the pathogenesis and treatment of tetanus is vast and confusing, the object of this report is to present a rational approach to the treatment of tetanus derived from personally observed cases, a review of the literature, and an analysis of 70 cases treated by various methods at Gorgas Hospital from 1905 to 1956.

The tetanus bacillus (Clostridium tetani) is a saprophytic organism having no invasive property and therefore tends to remain at the inoculation site. The bacillus causes disease by elaboration of a powerful water-soluble exotoxin during its proliferative phase; this toxin then leaves the focus of production to reach all tissues of the body and has the capacity of acting upon the central nervous tissue of susceptible animals to produce violent convulsions and death from asphyxia.

The route by which the toxin reaches the central nervous system (CNS) had long been postulated by Ransom and Meyers to be by centripetal spread via peripheral nerves, but this view was challenged by Abel et al., who demonstrated that toxin reaches the CNS via the blood stream. Although it is still a controversial issue, there is convincing evidence to support the hematogenous spread theory. Indirect evidence against the theory of spread by peripheral nerves is shown by the fact that regardless of where the focus of infection is located, the first presenting sign is trismus and the length of incubation period is not affected by the site of infection.

The action of the toxin is almost entirely on the nervous system; the only functional changes noted are convulsions and fever, both probably due to CNS effects. While other tissues may absorb the toxin, no functional or pathological alterations can be noted and postmortem tissue changes are meager and nonspecific.

In an infection of local nature which gives off a toxin that affects a remote system, several questions must be answered before a logical therapy can be developed: 1. How rapidly is toxin produced? 2. How rapidly is toxin absorbed and circulated? 3. What is a symptomatic and what is a lethal amount?

Toxin production obviously varies in different situations, governed by the size of the inoculum and how favorable an environment the wound provides. Even in our relatively small series, the incubation period (the time between the initial injury and the accumulation of enough toxin to produce symptoms) varied from 4 to 36 days. The amount of toxin in a patient cannot be measured with any accuracy. Even in most animal experiments the amount of toxin is assayed by biological rather than metric methods. From a clinical viewpoint, three levels of toxin can be postulated: (1) the minimal amount that will produce symptoms in the animal under discussion, (2) the minimal lethal dose in this animal, and (3)

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the maximum amount that can be absorbed by the animal's tissue. This third concept is of value only in understanding experimental data. The relationship between the minimal symptomatic and the minimal lethal amounts is most important. If only a small increment over the minimal symptomatic amount is needed to reach the lethal level, antitoxin therapy would have little value, since this lethal amount would be produced and fixed by the tissues before the diagnosis is made. If there is a wide difference between these levels, the effects of the toxin will be diagnostic and treatment can be started before the lethal level is reached.

In addition to the rate of production, the avidity or reluctance of absorption is important. Toxin from a wound probably rises by small increments rather than in one large quantity as is given in many animal experiments. Again, two contrasting conditions may be postulated. Susceptible tissue may take up toxin avidly, leaving little in the circulation exposed to neutralization. On the other hand, the toxin may require constant circulation and prolonged intimate contact with the tissues before absorption. Of course, the second situation would be more favorable for neutralization before a lethal amount has been fixed in the CNS.

There has been much discussion about the "latent period" of tetanus, and this should not be confused with the incubation period. The latent period is defined as the time required for production of symptoms after the toxin has been taken up and irrevocably fixed by the tissues. As long as toxin is circulated or is so loosely bound to the tissues that it can be neutralized by tetanus antitoxin, it is probably not initiating the functional changes that will produce symptoms. That a true latent period does exist is very obvious when patients are studied. Almost invariably, the disease becomes worse in the first 24 hours after diagnosis, even though large amounts of tetanus antitoxin are used.

Finally, a most important question from the therapeutic aspect is whether the patient who has fixed an ordinary lethal amount of toxin can still be saved by modification of the action of the toxin.

TABLE 1.—*Guinea Pigs Given Inoculations of the Sheep's Blood*

Day	Date	Sheep	Symptoms	Date	Result
1	10-30	Normal	0		
2	10-31	Normal	0		
3	11-1	Normal	+	11-5	Recovered
4	11-2	Normal	+	11-5	Recovered
5	11-3	Normal	+	11-5	Died
6	11-4	Normal	+	11-6	Died
7	11-5	Stiff neck	+	11-6	Died
8	11-6	Stiff neck	+	11-7	Recovered
9	11-7	Stiff neck	+	11-10	Recovered
10	11-8	Stiff neck	+	11-10	Recovered
11	11-9	Stiff neck	+	11-11	Recovered
12	11-10	Stiff neck	+	11-13	Recovered
13	11-11	Died	+	11-14	Recovered

A simple but significant experiment was conducted by McClintock and Hutchings, in 1913,[1] which answers many of the questions just raised and which served as a background in the formulation of our present concept of therapy. These investigators implanted splinters infected with tetanus spores in the tails of sheep. Blood was drawn daily and injected into guinea pigs. When the first signs of tetanus appeared in the sheep, the tails were amputated. In spite of this prompt removal of the source of toxin, all sheep died. A typical experiment is shown in Table 1. Interpretation of this experiment seems to answer several of the questions raised: 1. There appeared to be a difference between the minimal symptomatic and the minimal lethal quantities as several of the guinea pigs developed symptoms of tetanus from injections of 2 cc. of the sheep's blood and yet survived. 2. Unless it is assumed that the sheep's tissues were saturated with the toxin by the end of the second day and that there was a latent period of five days, it appears that tetanus toxin is only slowly taken up by the CNS. Data from an experiment of Abel[2] adds evidence that toxin is not rapidly fixed. If an amount of toxin described as 480 M. L. D. for guinea pigs was injected per kilogram of dog, fatal tetanus invariably followed. In one experiment, the dogs were

given 16.5 times this amount. The control animal died of tetanus in 48 hours. Exchange transfusions were begun on the other dog after eight hours and required two hours for completion. Only 54% of the total toxin could be recovered in this manner, yet 85,000 units of T. A. T. given immediately after the procedure prevented any symptoms of tetanus from appearing in this animal.

The sheep experiments of McClintock and Hutchings were continued with three groups of sheep. The first group of five sheep received 6000 units of T. A. T. immediately after amputation of the tail; this resulted in survival of one sheep. In the next group of five sheep, a sedative, intraperitoneal chlorbutanol, was used, with recovery of two sheep. Two died of chemical peritonitis, and the fifth died of chlorbutanol poisoning. The last group of five sheep received both T. A. T. (6000 units) and sedation with chlorbutanol after amputation of the tail. Four sheep survived, and the fifth died of peritonitis. (These experiments demonstrated that when animals are sedated sufficiently to prevent convulsions and death from asphyxia and protected with the neutralizing effect of tetanus antitoxin, they would survive despite the fact that the animals received many lethal doses of tetanus antitoxin!)

Analysis of Cases

At Gorgas Hospital from 1905 through 1956 there was 70 cases of tetanus other than neonatal. In general terms, the cases can be divided into four eras in accord with the therapy given. From 1905 through 1926, antitoxin was rarely used in amounts of 50,000 units or more; surgery, inadequate sedation, and small daily amounts of tetanus antitoxin comprized the form of therapy. From 1927 through 1945, at least 50,000 units of T. A. T. was usually administered; sedation was light, and no antibiotics were available. From 1945 through 1952, antibiotics were added to this regimen. The four cases from 1953 to 1956 received heavy sedation, tracheotomy, T. A. T., and penicillin. Three had surgery.

In the total of 70 cases, there were 41 deaths, or a mortality of 58%. When these figures are broken down, it is seen that from 1905 through 1926 there were 46 cases and 37 deaths, or an 80% mortality. When tetanus antitoxin was added in the era between 1926 and 1945, the mortality was 18.8%, or 3 deaths in 16 cases. From 1945 through 1954, antibiotics were added to the above and there were four cases with one death, or a mortality of 25%. From 1954 to 1956, heavy sedation was added and all four cases have survived. In the tabulation in Table 2, cases that received treatment described as that generally used in one era are included in that era no matter when the case actually occurred.

Treatment of Tetanus

It is apparent that there are three aspects to be considered in the treatment of tetanus: (1) local treatment, (2) treatment during the circulatory phase, and (3) treatment during the fixed phase.

Local Treatment.—Antibiotics, debridement, and amputation all have the objective of terminating toxin production. There is some question about the effectiveness of penicillin and the broad-spectrum antibiotics on tetanus organisms in vivo.[3] Undoubtedly, antibiotics are now used in all cases of tetanus. Any reduction of mortality could be attributed to the effect on C. tetani or to control of complicating infections, making it impossible to evaluate the role of sterilization of the local wound.

Debridement is frequently used, but at least in two series the mortality was not reduced.[4,5] Amputation should be more promptly and totally effective than either antibiotics or debridement, yet in experiments of McClintock and Hutchings, this did not affect the mortality.

A study of cases without known site of entry is provocative, since there is no local treatment other than antibiotics. In our series there were 17 such cases. Ten of

TABLE 2.—*Data on Cases from 1905 to 1956* *

Case No.	Year	Age	Site	Incubation	Surgery	Antitoxin	Result
			1905–1926				
1	1905	13	Foot	30		0	D
2	1905	23	Finger	7		0	D
3	1905	23	Leg	36		90 cc.	D
4	1907	34	Uterus	6		?	D
5	1907	35	Hand	8		?	D
6	1907	21	Foot	21		0	W
7	1908	28	Leg	10	Amputation	6,000	D
8	1908	26	Buttock	9			D
9	1908	28	Foot	15			D
10	1909	17	Foot	9		30,000	W
11	1909	40	Foot	4		18,000	D
12	1910	25	Foot	30		10 cc.	D
13	1911	32	?	?		15,000	D
14	1911	22	Heel	4		36,000	D
15	1911	30	Finger	6	Amputation	29,500	W
16	1912	39	Foot	19		21,000	W
17	1912	6	?	?		0	W
18	1912	43	Arm	11	Amputation	12,000	D
19	1913	26	Arm	14		0	D
20	1913	40	Hand	?		19,500	D
21	1913	24	?	?		18,000	D
22	1913	35	Scalp	7		24,000	D
23	1914	33	?	?		14,500	D
24	1914	26	Foot	?		29,000	D
25	1914	28	Hand	30		28,500	D
26	1914	42	Foot	8		42,000	D
27	1914	22	Foot	3		9,000	D
28	1915	22	?	?		6,000	D
29	1915	20	Leg	?		33,000	D
31	1916	22	Finger	14		38,000	W
32	1916	32	Finger	30		36,000	W
33	1917	24	Hand	21		27,000	W
34	1917	29	Finger	14		12,000	D
35	1918	35	Hand	6		12,000	D
36	1918	24	?	?		30,000	D
39	1919	12	?	?		12,000	W
40	1920	46	Foot	7		15,000	D
41	1920	9	Foot	8		18,000	D
42	1922	7	?	?		0	D
43	1923	29	Toe	10	Amputation	39,000	D
44	1924	5	?	?		9,000	D
45	1926	33	Scalp	9		16,000	D
48	1929		Finger	7	Amputation	30,000	D
51	1931	63	Heel	8		33,000	D
52	1932	27	?	?		40,000	D
64	1947	55	Leg amp.	?		0	D
			1926–1945				
30	1915	40	Foot	10		60,000	D
37	1919	10	?	?		99,000	W
38	1919	36	Foot	6		60,000	W
46	1927	31	Foot	11		70,000	W
47	1928	2	?	?		60,000	W
49	1929	5	?	?		50,000	W
50	1931	9	Foot	15		60,000	W
53	1935	13	Leg	8		90,000	D
54	1937	12	?	?		560,000	W
55	1938	24	Foot	14		200,000	W
56	1939	53	Ankle	8		125,000	W
57	1940	54	?	?		340,000	W
58	1942	31	?	?		180,000	W
59	1942	14	Hand	13		210,000	W
60	1943	8	Foot	?		70,000	W
61	1944	3	Burns	13		120,000	D
			1945–1952				
62	1945	10	Hip	4		70,000	D
63	1945	56	Leg ulcer	?		200,000	W
65	1949	36	Abortion	9		170,000	W
66	1952	13	?	?		500,000	W
			1953–1956				
67	1953	29	Abortion	?	Hysterec.	190,000	W
68	1955	29	Abortion	14	Hysterec.	200,000	W
69	1956	26	?Uterus	?	Hysterec.	180,000	W
70	1956	48	?Foot	?		50,000	W

* Cases that received treatment described as that generally used in one era are included in that era no matter when the case actually occurred.

these cases received less than 50,000 units of T. A. T., and only two recovered. Seven cases received more than 50,000 units of T. A. T., and all survived. Only one of these seven patients had antibiotics. It appears that toxin is not produced indefinitely, and if it is effectively neutralized, the local infection will be overcome as are other such infections.

Thus, we conclude that the local lesion should be handled as would be warranted if tetanus were not present.

Antitoxin in the Circulatory Phase.—It has been shown that if sufficient T. A. T. is mixed with many lethal doses of tetanus toxin, this toxin is so modified that its injection causes no symptoms. Spaeth [4] found that T. A. T. maintains an adequate level of antitoxin from two to four weeks and that 50,000 to 60,000 units is sufficient in most cases of tetanus.

Addition of at least 50,000 units of T. A. T. reduced the mortality in the Gorgas Hospital cases from 80% to around 20%. It seems that many cases can be treated when sufficient toxin has been absorbed to produce diagnostic symptoms and yet before a lethal amount has been fixed.

Treatment of the Fixed Phase.—The mode of death in experimenttal and clinical tetanus is frequently convulsions and death by asphyxia. When the experimental sheep were sedated below convulsive levels by McClintock and Hutchings, many of the animals survived. A review of the Gorgas Hospital cases revealed that approximately 45% of the patients had convulsions and died in apparent respiratory failure. The tetanus patient has severe muscular contractions or spasms, which can produce laryngeal spasms, making respiration difficult, and produce death by asphyxia. The major objective of therapy then is the prevention of convulsions by adequate sedation. When emphasis on heavy sedation to prevent convulsions was made and instituted into the therapeutic regimen at Gorgas Hospital, all four cases of tetanus survived. The number of cases treated in this manner is exceedingly small, but the rationale for sedation appears clear, as it eliminates these deadly convulsions. A technically difficult method is available, using curare and the Drinker respirator, but this would require at least 10 days or more of curare. Barbiturates are the type of sedation most familiar to the physician. In the Gorgas Hospital cases, intramuscular phenobarbital sodium in sufficient amounts to relieve muscle spasm and intravenous amobarbital (Amytal) sodium were used when needed immediately to prevent convulsions. In the heavily sedated or comatose patient, the airway assumes major importance. As obstruction to the airway can occur and produce asphyxia, a tracheotomy performed prophylactically will prevent this complication and allow the bronchial secretions to be eliminated more easily by tracheal suction. These secretions can easily be brought into the major bronchi and trachea by gravity. Shock blocks placed under the foot of the bed will produce sufficient effect to allow secretions to gravitate into the area where suction can be applied effectively. The danger of aspiration during a convulsion is not so likely after a tracheotomy. Tetanus produces its maximum effects for more than 10 days, so that the patient must be sedated below the convulsive levels for a like period, prior to allowing the patient to return to full consciousness. Often the cumulative effects of the barbiturates are such that the patient will be unconscious for a longer period of time. During this time, the tracheotomy allows an adequate airway and the unconscious patient can be maintained fairly safely. Although many of the records are not specific, they showed that only 45% of the patients died as a result of convulsions and asphyxia and they do not record the terminal event in 55% of the cases. If the patient dies by circulatory collapse or central respiratory failure, then it is obvious that in these cases sedation will be of no value. This is a critical point for future investigation. However, the rationale for sedation is clear in eliminating the convulsions.

Case Presentations

Our interest began when Case 67 was treated here. This patient had treatment to the local wound and to the circulatory and the fixed phases. Her survival influenced the treatment of the following two cases. The experience in Case 69 provoked a re-examination of the basic pathophysiology, and the last case was treated by what we consider a more rational method.

CASE 67.—The patient is a 29-year-old woman who was admitted to Gorgas Hospital on May 19, 1953, with the diagnosis of tetanus. The previous day she had been at another hospital complaining of difficulty in breathing and trismus. At first it was thought that she had hysteria, but when convulsions began a diagnosis of tetanus was made and she was transferred to this hospital. It later developed that she had induced an abortion 14 days prior to the onset of symptoms. On admission she was having tetanic convulsions, and a foul vaginal discharge was present. The patient was started on sedation and penicillin. The following day a tracheotomy was performed. The patient's convulsions were controlled, but she began to run a fever, with temperature to 104 F. On the 15th day, after much debate, a total hysterectomy was performed to remove the site of infection. After surgery, her fever continued for 21 more days but her course was complicated by pneumonia and a urinary infection. Her survival was in doubt during most of this period, but she finally made a complete recovery. The uterus was cultured, but no tetanus organisms were recovered. The pathological report showed necrosis of the endometrium in the fundus and inflammation in the underlying myometrium. Apparently, hysterectomy removed an infection uncontrolled by multiple antibiotics. While unproven, it was felt that the infection with tetanus was also uncontrolled due to the nature of the wound and that continuing liberation of toxin contributed to her fever and toxicity. However, convulsions were completely controlled from the first day.

CASE 68.—The patient is a 29-year-old woman who was admitted to the hospital because of inability to open the mouth. At first this was felt to be due to a dental infection. Later, other muscle spasms were noted when the diagnosis of tetanus was made. It was found that she had induced an abortion 14 days before the onset of symptoms. On the day after admission, when the diagnosis of tetanus was established, she was given 200,000 units of tetanus antitoxin, penicillin, and heavy sedation, and prophylactic tracheotomy was done. Later the same day a hysterectomy was performed. The patient developed a fever, with temperature to 102 F on the day after surgery. This fever persisted for eight days. Pathological examination of the uterus showed acute inflammation of the site of the placental attachment but no inflammation of the underlying myometrium. Elsewhere the uterus was essentially normal. She made a complete recovery. Prompt hysterectomy was performed because of the experience in the previous case. Probably this infection could have been handled by antibiotics; certainly the hysterectomy would have been postponed if there had been no tetanus. Her course was relatively benign.

CASE 69.—The patient is a 26-year old woman who was admitted to the hospital with a diagnosis of tetanus when she consulted a physician because of trismus. No history of abortion was obtained, although she had missed one menstrual period and had been having vaginal bleeding for about two weeks, for which she inserted a cotton pack in the vagina. It is interesting that this patient received three tetanus immunizations less than one year before admission. Immediately after admission the patient was given 180,000 units of T. A. T. and was sedated heavily, and a prophylactic tracheotomy was done. On the day of admission, a hysterectomy was performed to remove the site of infection. Pathological examination showed a 10-week-pregnant uterus, with occasional small areas of erosion of the endocervical epithelium and slight superficial polymorphonuclear infiltration. As stated, the experience with this case provoked our present ideas and this presentation. Without tetanus being present, there would have been no justification for hysterectomy. The uterus was not grossly infected, and antibiotics should have cleared the infection seen. The hysterectomy was done because our idea at that time was that the local wound should be debrided or removed to eliminate the source of toxin. It is only fitting to observe that a deep site of tetanus infection is much more difficult to evaluate and manage than a site that can be inspected. All cases of tetanus are febrile, and this fever lasts from 8 to 14 days. In the case of a deep infection, one cannot be certain whether this fever is due to the central effects of the toxin or to uncontrolled associated infection. The patient developed a fever to 104 F the day after surgery and became afebrile only after 10 days. Convulsions were prevented with adequate sedation, and she made a complete recovery.

CASE 70.—The patient is a 48-year-old leper who had had ulcers on the legs for many years. On the day before admission he had difficulty in opening his mouth and was admitted to the hospital. The following day, definite signs of tetanus were seen. Immediately after diagnosis, the patient was sedated heavily and given 50,000 units of tetanus antitoxin and a prophylactic tracheotomy was performed. No local treatment to the leg ulcers was administered. Convulsions were controlled

with heavy sedation of phenobarbital. However, his temperature rose to 104 F on the third day of hospitalization and he remained febrile for a total of 14 days. He made a complete recovery.

Summary

The treatment of tetanus can be directed at the three aspects of the disease: at the local wound, at the circulating toxin, and at the effects of fixed toxin. This report presents experimental data from the literature, an analysis of cases treated over a period of 50 years, and a presentation of four recent cases. From these, a seemingly logical approach to therapy has been devised.

Apparently, treatment directed to the local wound has little effect on the outcome in a case of tetanus. The wound should receive only the attention warranted if tetanus were not present.

Circulating toxin is not avidly fixed by the tissues, and in many cases neutralization can be accomplished before a lethal amount has been fixed.

Fixed toxin acts on the central nervous system (CNS), giving fever, convulsions, and asphyxia. Proper sedation can prevent these convulsions, but the length and depth of the required sedation make a prophylactic tracheotomy mandatory.

Gorgas Hospital.

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Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. Archives of Internal Medicine, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

Oral Hypoglycemic Agents Past and Present

Other Than Sulfonylurea Compounds

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The successful introduction of the hypoglycemic sulfonylureas has aroused new interest in the attempts of the past to develop oral antidiabetic agents and has stimulated a new search for other substances with similar action. A historical review of this long series of failures and near successes would probably have little more than academic interest if it did not illustrate at the same time the vagaries of scientific progress. Discoveries usually lead to progress only if they are made at the right time. Commonly their acceptance depended on the readiness with which they can be integrated into prevalent thought, knowledge, and practice. The hypoglycemic sulfonylureas were discovered at such a fortuitous time. Even though originating from a chance observation, they were readily accepted because our concept and knowledge of diabetes had changed. A functional and multiple etiologic theory had replaced the old concept of an organic islet-cell deficiency. It had become conceivable that aside from insulin other modalities might offer a rational and perhaps even a causal therapy. In the light of this changed concept of the disease, some of the old approaches may now gain new aspects and invite reinvestigation.

The present review is based on some of our own experiences, but largely on the literature.[1-5] It is subdivided into three parts: I. Empiric drugs, with a comment on oral insulin preparations; II. Plants, plant extracts, and plant hormones; III. Chemical compounds other than sulfonylureas with marked oral hypoglycemic action, particularly the guanidine derivatives.

I. Empiric Drugs

The pharmacopoeia of the latter part of the last and the early present century contained numerous drugs which empirically had been found to influence beneficially the diabetic glycosuria if not the hyperglycemia. Most of them were hypnotics or sedatives, analgesics and antipyretics, digestive enzymes, or drugs affecting the autonomous nervous system and heavy metals as arsenics. Antihistaminics and vasodilators have been added to this list only recently. These deserve a brief comment, as well as the pancreatic enzymes and the salicylates, which have had a recent revival.

Digestive Enzymes.—Replacement therapy with pancreatic enzymes is certainly

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indicated in surgical diabetes. It substitutes for the loss of the external secretion of the pancreas, improves the general nutrition, and indirectly affects the severity of the diabetes. No evidence, however, exists about impairment of the excretory function of the pancreas in diabetes mellitus of man or of a specific effect of pancreatic or digestive enzymes on the diabetic hyperglycemia or glycosuria. The insulin-sparing effect recently claimed for a new enzyme preparation [6] is most likely as unspecific as that of the enzymes used formerly. If it is significant at all, it is due to the imponderabilia of the attendant careful supervision and dietary control.

Vasodilators.—The same seems to be true for the ameliorating effect of vasodilators on diabetes. This has been observed in patients under such treatment because of peripheral vascular complications, particularly leg ulcers.[7-9] The development as well as the improvement of these lesions, like that of most other diabetic complications, is reflected in an aggravation and subsequent amelioration of the disease. Thus, the therapeutic effect of vasodilator agents on the peripheral vascular lesions will be commonly accompanied by a decreased insulin requirement or a decreased glycosuria. Where the drugs do not affect the complicating vascular lesions, or if they are given in the absence of any complication, the diabetic state is usually unaltered. With Zarowitz,[10] I have demonstrated that tolazoline (Priscoline) hydrochloride has no significant influence on the blood sugar of nondiabetic healthy persons. An increased production or secretion of insulin subsequent to better pancreatic circulation due to a specific action of the vasodilators seems therefore to be most unlikely.

Antihistaminics.—The well-established hyperglycemic effect of histamine led naturally to an examination of a possible influence of the antihistaminics on carbohydrate metabolism. Moreover, the side-effects of these substances, such as tremor, perspiration, headaches, and mental cloudiness, suggested the possibility of hypoglycemia. Mild lowering of the blood sugar was found in both man and the experimental animal with some preparations but not with all. Those found to be effective were tripelennamine (Pyribenzamine), N-benzyl-N′,N′-dimethyl-N-phenylethylenediamine (Antergan), and antazoline (Antistine).[11-13] Together with Jauregui,[14] I have carried out a clinical evaluation of the latter substance and could demonstrate that oral administration of rather large doses (500-600 mg. per day) had indeed a significant effect on the diabetic hyperglycemia and glycosuria. This effect was about equal to that of the 20-30 units of long-lasting insulin. Smaller doses were ineffective, and still larger doses did not increase the effect. The doses required were not always free from the typical side-effects of the antihistaminics. The clinical usefulness of this medication was thus limited not only to patients with a rather small insulin requirement but furthermore to those who could tolerate relatively large doses. On the other hand, in the treatment of allergies in diabetic patients, the "hypoglycemic" antihistaminics may deserve preference over related preparations without effect on the glycemia.

The mechanism of the hypoglycemic action of these antihistaminics is obscure. Since the effect is not shared by all antihistaminics, it is unlikely that it is due to inhibition of histamine. A nonspecific effect such as that seen after phenobarbital and other sedatives is also unlikely, since the hypoglycemia after sedatives is considerably smaller. There is some evidence of absence of the antihistamine effect in totally depancreatized animals. Therefore, an action via the pancreas or a dependence on the presence of insulin has been suggested. Attention has also been called to structural similarities between some antihistamines, as for instance, tripelennamine and guanidine, which might invite speculation about similarity in action.[12]

Salicylates.—Acetylsalicylic acid was used widely in the management of diabetes in the preinsulin era. It had been known for long to have a hypoglycemic effect. This has found new interest because it is one of the features in which the salicylates differ from corticotropin (ACTH) and the corticosteroids, with which they share so many other aspects. Diabetic patients suffering from rheumatic fever were found to have markedly decreased insulin requirements when treated simultaneously with large doses of acetylsalicylic acid, while the steroids so often increase the insulin requirement. Nondiabetic children with rheumatic fever may show moderate hypoglycemia under salicylate medication.[15] Reid and his associates,[16] in England, reexamined this effect in uncomplicated diabetes. Daily medication of 5 to 10 gm. of acetylsalicylic acid decreased significantly the hyperglycemia and glycosuria and was also capable of abolishing ketonuria. None of these patients was receiving insulin. Salicylate treatment without insulin abolished fully the diabetic symptoms of thirst, polyuria, and pruritus, but it caused the expected side-effects of tinnitus and impairment of hearing. Glucose-loading tests showed marked improvement of the glucose tolerance by acetylsalicylic acid and suggested increased glucose utilization.

These clinical observations have found corroboration in animal experiments. Ingle showed that the glycosuria of partially depancreatized rats improved markedly by oral or parenteral administration of 40-160 mg. per day of acetylsalicylic acid.[17] He suggested that the salicylates suppress adrenal cortical function, since similar amelioration of the diabetes can be induced by adrenalectomy. Interesting as this rediscovery of the hypoglycemic action of salicylates is, acetylsalicylic acid is not likely to become again an oral antidiabetic agent. Its relatively low efficiency even in large doses, on the one hand, and the dangers of salicylism, on the other, will prevent its clinical use.

Estrogens.—Mention should be made here of estrogenic hormones as hypoglycemic agents. The empiric observation that the onset of diabetes in females coincides often with the onset of the menopause lead to therapeutic trials with estrogens. It was found, indeed, that sustained hypoglycemia can be induced with large doses of estrogens, i. e., 50,000 to 80,000 R. U. This effect is thought to be due to a depression of anterior pituitary action. It is, however, usually too weak as to replace insulin and, moreover, rather unreliable and unpredictable. Small doses of estrogens frequently cause hyperglycemia. Nevertheless, control of diabetes has been reported either with the hormone alone or in conjunction with insulin.[18,19]

Oral Insulin Preparations.—Innumerable attempts have been made to produce an orally effective insulin preparation.[1] All such attempts have met with failure. Gastric or intestinal digestion of the hormone could not be prevented by combinations with saponins, bile, hexylresorcinol, or trypan red and malachite green. Likewise, sublingual insulin preparations, suppositories, sprays for inhalations, or salves for percutaneous administration have been universally ineffective.

II. Plants, Plant Extracts, and Plant Hormones

Folk medicine all over the world included the use of many plants and plant extracts for the treatment of diabetes mellitus. After the discovery of insulin, the attempts to evaluate these remedies and to isolate a hypoglycemic principle were spurred for a considerable time. It was hoped that an insulin-like substance might be present not only in the vertebrate organism but also in plants and lower organisms wherever carbohydrates are metabolized. Collip's glucokinin, a yeast extract, was only the first of a long series of substances which were reported to have hypoglycemic activity and therapeutic usefulness.[1,2] Some others should be mentioned, such as phaseolin, out of beans and bean pods; myrtillin, out of blueberries; antimellin, out of the jambul fruit; lupanine out of Lupinus albus, and

galegine out of Galega officinalis. This latter substance is of special interest because it is an iso-amyl-guanidine. Most of these substances were found either to be entirely ineffective in human diabetes or to have so little hypoglycemic activity that they did not compare at all with the efficacy of insulin. Moreover, in the depancreatized dog, which for so long was the standard test preparation, none showed any promise. Because of these disappointing results, the field was soon abandoned and new claims for plant extracts with insulin-like action were looked at suspiciously and often discarded without careful evaluation.

In the meantime, we have learned from the aryl-sulfonylureas that a compound may be ineffective in experimental diabetes after pancreatectomy or alloxan poisoning and yet be therapeutically useful in clinical diabetes. Its beneficial action may even depend on the presence of the pancreas and its hormone, even though these may be impaired. It may be capable of enhancing insulin activity, of inhibiting its peripheral degradation, or of stimulating its production or secretion. This new concept alone should be a theoretical reason for reexamination of some of the old plant extracts. There are, however, other reasons: In recent years new extracts with uncontested hypoglycemic action have been prepared and an unexpected link between plant hormones and insulin activity has been uncovered.

Let us consider first the new plant extracts.

1. *Hypoglycin.*—Ackee, the chestnut-like fruit of Blighia sapida, a native tree in the West Indies, had long been known to cause severe "vomiting sickness," convulsions, and unconsciousness if ingested when not yet ripe. Only a few years ago it was found that part of the syndrome is due to hypoglycemia and will respond to glucose administration.[20]

In 1954, Hassal, Reyle, and Feng [21] isolated from these fruits two polypeptides with marked hypoglycemic activity, which they called hypoglycin A and B; the latter was about half as effective as the former. Studies by Chen and his associates,[22] as well as by Leppla and von Holt,[23] confirmed that both substances were hypoglycemic but also emetic when administered parenterally or orally to many animal species, such as the mouse, rat, rabbit, guinea pig, cat, and dog, as well as in man. Both functions seemed to be linked to each other except in the pigeon, where the emetic dose did not alter the blood sugar level.

The effect of hypoglycin does not seem to depend on the presence of the pancreas nor to be mediated through the adrenals; alloxan-diabetic and depancreatized animals respond as well as adrenalectomized animals, although somewhat less than the intact animal.

The livers of treated animals show marked fatty degeneration and decreased glycogen content. Contrary to insulin, the isolated diaphragm does not show a glycogen increase when incubated with hypoglycin. As would be expected with an agent with extrapancreatic action, the α- and β-cells of the islets of Langerhans are not significantly altered by the administration of these substances. Yet the possibility has not been ruled out entirely that hypoglycin owes a part of its activity to its stimulation of the islet cells.[23]

The clinical usefulness of hypoglycin must be held in doubt until we know more about its mode of action and about the possibility to separate the emetic from the hypoglycemic activity. Progress has been made in this direction by further purification of the two active substances and by the demonstration that both contain a hitherto unknown amino acid which apparently represents the hypoglycemic principle.[24] According to this analysis, hypoglycin B is a peptide of hypoglycin A and glutamic acid; hypoglycin A, however, is not a peptide but an amino acid of the structural formula of $C_7H_{11}N_1O_2$ and a molecular weight of 141.

Corchorus Olitorius.—Another substance which appears to enhance insulin and to be

ineffective in the absence of the pancreas has been extracted a few years ago from the leaves of a hemp variety, Corchorus olitorius.[4] The original findings reported by French scientists in Tunisia[25] do not seem as yet to have been reexamined. But it appears that a water-soluble substance was obtained which was free of N; which contained traces of sulphur and of zinc; which was capable of lowering the blood sugar of intact mice, guinea pigs, and rabbits; which protected at least partially against alloxan diabetes, and which enhanced the effect of subthreshhold doses of insulin. This substance caused an increase in liver glycogen. Hemp leaves have been a folk medicine in Tunisia for many centuries. They may still yield some useful remedy.

Aspergillin.—A third apparently as yet unexplored hypoglycemic substance is supposed to be present in Aspergillus niger.[4] Its extracts are reported to be entirely free of toxic side-effects and to have a powerful hypoglycemic activity both in intact and in alloxan-diabetic rats on oral and parenteral administration.[26] They, too, may deserve further evaluation.

Insulinase Inhibition and Plant Hormones.—In his work on enzymatic degradation of insulin, Mirsky[27] made the basic discovery of hypoglycemic action of plant hormones and plant growth regulators. He started from the old observation that insulin loses its hypoglycemic activity when incubated with blood and particularly with liver tissue.[29] In attempts to isolate this contrainsulin principle, he found that liver tissue contains not only an insulin-destroying or inactivating factor but also another factor which is capable of inhibiting the first one.

The insulin-destroying factor of liver showed all characteristics of an enzyme. The question whether this enzyme is insulin-specific and whether it deserves the name insulinase is of no importance here, where interest centers around that liver factor which inhibits enzymatic insulin degradation and which is capable of enhancing insulin activity, the so-called insulinase inhibitor. This factor was found to be present in a nonprotein fraction of liver tissue and at first appeared to be a peptide. In studying the effect of various protein dialysates on the destruction of insulin by liver extracts, Mirsky found that the amino acid L-tryptophan and some of its derivatives showed the same activities. They were insulinase inhibitors in vitro and hypoglycemic agents in vivo. The hypoglycemic effect could, however, be obtained in the intact animal only. No hypoglycemia could be induced in the alloxan-diabetic animal, indicating that the presence of insulin is necessary for this effect of L-tryptophan and its related compounds. Oral or parenteral administration of tryptophan derivatives, such as indol-3-acetic acid, nicotinic acid, and anthranilic acid, had about the same effect on the blood sugar of the intact animal and on insulinase activity. They too were not hypoglycemic in the alloxan-diabetic animal.

Remarkable as this observation is in itself, it gains in importance as indol-3-acetic acid and some of the other tryptophan derivatives are either natural or synthetic plant-growth regulators. Indol-3-acetic acid itself is the major natural auxin or plant growth hormone.[30]

No conclusive clinical evaluation of these findings has been made as yet. Indications are that not all animal species respond in the same fashion to L-tryptophan or its related compounds. In the dog, for instance, according to Mirsky, indol-3-acetic acid causes only a minimal decrease of the blood sugar. It will, however, enhance the insulin activity. If administered simultaneously with insulin, the hypoglycemia is significantly severer than after insulin alone. I have given doses of 3 gm. per day of nicotinic acid to diabetic patients and have not observed any alterations of the fasting blood sugar. Others have seen both hypoglycemia and hyperglycemia after medication of various doses of nicotinic acid or related compounds.[9,28] If overactivity of

insulinase is the cause of some form of maturity-onset diabetes which is characterized by an adequate islet-cell system and adequate insulin production, a beneficial effect should indeed be expected from agents which inhibit peripheral insulin destruction.

III. Chemical Compounds Other Than Sulfonylureas with Marked Oral Hypoglycemic Action

Sulfur Compounds.—The aryl-sulfonylureas are the first clinically acceptable orally effective hypoglycemic agents. Other sulfur compounds have been known for some time to affect carbohydrate metabolism. It is indeed surprising that the hypoglycemic sulfonylureas owe their discovery to a chance observation and not to systematic research. Such research was initiated by the findings that insulin as well as the pancreatic islets contain large amounts of sulfur and that sulfur-containing substances, such as cystine, cysteine, and glutathione, play an important role in carbohydrate metabolism.[3] It led to the discovery that these latter substances can protect the experimental animal against alloxan diabetes and initiated therapeutic trials in human diabetes. Various sulfur preparations, particularly thiourea and many of its derivatives, were found to induce decrease in hyperglycemia, glycosuria, and ketonuria. This effect, however, was less marked than that of insulin but also less than that of the aryl-sulfonylureas. Like in the case of these latter compounds, the effect of the other sulfur preparations was absent after total pancreatectomy and appeared to enhance the action of insulin. The mode of action of these substances was thought to be due to an increase of glutathione and sulfhydryl groups in the tissues, which was to effect in the pancreatic islets increased insulin production and in the peripheral tissues acceleration of glucose oxidation.[31]

Guanidine Derivatives.—Synthalin: Guanidine had been found to be hypoglycemic by Watanabe.[32] This was one of the usually so fruitful scientific chance observations. Watanabe was studying parathyroid function. The Breslau School of Medicine tried to apply this observation to the therapy of diabetes mellitus. Galegine, the natural isoamyl-guanidine, and a number of synthetic guanidine derivatives were studied by both the pharmacologists and the clinicians.[33-35] Most were found to have toxic side-effects in addition to the hypoglycemia, causing convulsions irreversible by glucose administration and sudden death. The deca- and dodeca-methylene-diguanidine, however, appeared to be fairly safe, inasmuch as their hypoglycemic doses were far below the L. D_{50}. They were introduced as antidiabetic agents by Frank, under the name of Synthalin A and B.[36]

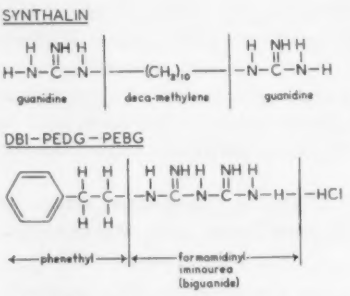
Synthalin, in contradistinction to the sulfonylureas, appeared at an inopportune time. At first it seemed to find a good clinical response. It was soon found, however, that the results could not stand a comparison with insulin, which just had revolutionized the management of diabetes. While insulin was universally effective, Synthalin, like our present-day oral hypoglycemic agents, could be used only in the mild or moderately severe diabetes of adult life. Its maximal efficiency equalled about that of 20-30 units of insulin per day, not unsimilar to the insulin equivalent of the sulfonylureas. Moreover, it had both toxic and unpleasant side-reactions. The latter were bad taste, loss of appetite and often vomiting, and gastrointestinal discomfort. More serious was the occurrence of liver damage. A number of instances of jaundice and hepatitis were reported in diabetics under Synthalin treatment. When fatalities due to acute yellow atrophy occurred, further clinical application was discontinued abruptly and the drug was held responsible for these serious complications. Surprisingly, the literature of these years contains very little documentation of these serious toxic reactions.[37,38] Frank and Wagner[36] list, in their review of 1932, hepatic damage as a contraindication and cite a few instances where liver disease preceded Synthalin medi-

cation but express the belief that the clinically recommended doses were toxic only to a previously diseased, not to a healthy, liver.

Other and perhaps more important causes for the withdrawal of Synthalin from clinical use were the results of studies in the experimental animal and in isolated tissues. These[39,40] seemed to suggest that Synthalin is a protoplasmatic poison which inhibits cellular respiration and causes anaerobic glycolysis with lactic acid accumulation. Since no evidence of increased glucose utilization could be found, and since the O_2 consumption did not increase, the Synthalin hypoglycemia was interpreted as sign and symptom of this cellulotoxic process. It must be stated, however, that most of these studies were done with doses far greater than those recommended for clinical use.

Synthalin has received interest again because of the newer hypoglycemic guanidine derivatives but also because of the discovery of its specific toxic effect on the pancreatic α-cells.[41] Since the α-cells are thought to be the site of production and secretion of glucagon, the hyperglycemic-glycogenolytic pancreatic factor, the suggestion was made that inhibition of glucagon was the primary mode of action of Synthalin. That this is unlikely is shown by the fact that Synthalin is effective even in the pancreatectomized animal.[42] Further studies have demonstrated that the α-cell degeneration can be found in many instances of toxic liver damage or liver disease and that it does not bear any relationship to hypoglycemia.[43] The α-cell changes after Synthalin administration thus may confirm the hepatotoxic potentials of this substance but do not explain its hypoglycemic activity.

DBI: New hypoglycemic guanidine derivatives are under investigation at present. The best known among them is DBI, PEDG, or PEBG, a phenylethylbiguanide. It differs structurally from Synthalin, which is a diguanidine, in which the methyl groups link two widely separated guanidines. In DBI,



Hypoglycemic guanidine derivatives.

the two guanidine molecules share a single amino nitrogen (Figure).

This moiety is said to form a stable chelate ring containing only five N atoms. While this structural change does not affect the hypoglycemic activity, it is thought to decrease the danger of liver damage. Indeed, no liver impairment has as yet been reported in man or experimental animals with clinically recommended doses. Large doses, however, have been found to induce in the experimental animal pathological alterations which are reminiscent of those caused by Synthalin, though less marked. Evidence of α-cell degranulation, hepatic glycogen depletion with moderate fatty infiltration, and occasional cellular necrosis has been noted.[44] Some other similarities with Synthalin have also been established. DBI, too, does not seem to require for its action the presence of insulin or of the pancreatic β-cells and is hypoglycemic in severe alloxan diabetes; it, too, shows a species specificity: man, rhesus monkey, and the guinea pig are most susceptible to its hypoglycemic action; then follow, in descending order, rat, cat, rabbit, and dog,[45] and it, too, may cause gastrointestinal disturbances, such as anorexia, nausea, vomiting, general malaise, and occasionally diarrhea.

In clinical trials DBI has been found to be effective in controlling hyperglycemia and glycosuria in the moderately severe disease.[46-48] Although no true dose equivalent for insulin has been established, it seems that in patients with a daily insulin require-

ment up to about 30 units DBI will be equally effective in doses between 100 and 200 mg. per day. While 100 to 150 mg. per day is usually well tolerated, undesirable gastrointestinal side-effects occur with rapidly increasing frequency with higher doses and limit seriously the clinical usage of the drug. If tolerated, DBI is, however, effective both in growth-onset or juvenile diabetes and in maturity onset diabetes. Moreover, there are indications of a special value of DBI in the management of brittle diabetes.[50] This relatively rare form of the disease which is characterized by frequent fluctuations of the hyperglycemia, has been most difficult to control with insulin, and usually does not respond to the sulfonylureas. Here the combination of insulin with DBI appears to permit stabilization of the glycemia.

These rather encouraging preliminary clinical observations may pave the way for a reintroduction of hypoglycemic guanidine derivatives as therapeutic agents in the management of diabetes; much will, of course, depend upon the results of the investigations in their mode of action and on the possibility of counteracting the undesirable side-effects.

What is known about the mode of action of DBI so far can be summarized as follows: DBI is not a insulin substitute in the sense that it acts like insulin. From the work of Williams and his associates,[47,51-53] we know that in therapeutic doses it neither stimulates insulin production or secretion, nor does it inhibit degradation of insulin or enhance its action. It does not inhibit the action of glucagon. While it decreases the blood sugar level and the glycosuria, the rate of glucose oxidation does not appear to increase. Contrary to insulin, it does not increase CO_2 production, nor does it increase the respiratory quotient. It decreases the glucose output from the liver, prevents gluconeogenesis, and increases glucose uptake by the muscle, but contrary to insulin, it does not accelerate glycogen deposition in the muscle. Instead, it causes increased lactic acid production. In liver slices incubated with DBI, the glycogen content decreases, while not glucose but lactic acid increases in the medium. Likewise, lactic acid increases and glucose decreases in the medium of the isolated diaphragm, while the diaphragm itself shows a decrease of both glycogen formation and O_2 uptake. In adipose tissue it decreases glucose oxidation and the conversion of glucose to glycogen and total lipid.[54]

All this goes to indicate that DBI and its related compounds inhibit oxidative carbohydrate metabolism and accelerate instead anaerobic glycolysis. In short, their action appears to be an inhibition of cellular respiration. Indeed, enzyme studies have indicated that the compounds block either the cytochrome oxidase [55,56] or the succinic oxidase.[57] If this turns out to be the mode of action of DBI, its practical usefulness would depend on the ability of the tissues to withstand this effect and on the ability of the organism to dispose of the increased lactic acid. Preliminary clinical observations have shown indeed an increase in the fasting and postprandial blood lactic acid level, as well as increased urinary excretion of lactic acid in patients under DBI medication.[58] Yet, no significant damage seems to have occurred after even prolonged medication.

In view of the earlier experiences with Synthalin there appears to be understandable caution against guanidine compounds. General rejection of the new compounds simply because they are guanidine derivatives and thus toxic is, however, most unjustified. DBI not only differs structurally from Synthalin and has proven so far to be free of hepatotoxic effects, but it must be remembered also that other guanidine derivatives have been employed successfully in the management of diseases. Paludrine is one of the most effective and safe antimalarial agents. It is N_1-*p*-chlorophenyl-N_5-isopropylbiguanide.[59] Moreover, without depreciating the need and the importance of understanding of mechanisms of clinically employed drugs, one should not forget that

even the mode of action of insulin is still not fully understood, more than 30 years after its introduction into the clinic.

Mesoxalic Acid: Before closing, I have to mention briefly another substance recently proposed as a hypoglycemic or antidiabetic agent—mesoxalic acid, or calcium mesoxalate.[60] Japanese investigators had found that this substance was capable of reducing the diabetic hyperglycemia in alloxan diabetes but not in the depancreatized animal. They concluded that mesoxalic acid stimulates β-cell function and insulin production. On the basis of this evidence, they applied it in the management of clinical diabetes and presented some evidence of improved glucose tolerance test. The few observations made in this country have been rather disappointing. Far more studies will be necessary before it can be decided whether this material deserves a place among the effective hypoglycemic agents.

Summary

Of the long series of the most diverse substances for which hypoglycemic activities have been claimed in the past, only a few appear to have any significant effect. None of these acts like insulin, and none can therefore be considered as an insulin substitute. Some appear to stimulate insulin production or secretion; others, to enhance its peripheral activity, probably by inhibiting its enzymatic destruction; still others seem to act on the cellular metabolism in the periphery. Toxicity or harmful side-effects will preclude the clinical application of some of them. But clinical evaluation, wherever possible, is warranted in spite of the availability and proven efficacy of insulin.

Since the etiology of diabetes mellitus is unknown and since it appears likely that peripheral factors may play a role in it as well as the primary deficiency of the insulin-producing islet-cell system, such evaluation may lead to a rational and possibly causal therapy for at least some type of the disease.

As yet, the aryl-sulfonylureas are the only substance of this group which have been proven to be useful in the management of one well-defined sector of diabetes mellitus. The presently available evidence raises similar hopes for the hypoglycemic biguanides.

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Contributions of Basic Science to Modern Medicine

Biliary Cirrhosis

Differential Features of Seven Types

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Biliary cirrhosis * is a pathologist's term to describe a simple pattern of cirrhosis within the liver characterized by an increase of fibrous tissue in the portal areas, a variable degree of bile stasis, and a preservation of the lobular pattern. A number of different diseases may give rise to this pattern. Each of these diseases within the liver has certain characteristics of its own that enable one to distinguish several types of biliary cirrhosis. In other words, biliary cirrhosis is a collective term to include several types of liver disease. The purpose of this report is to describe briefly the characteristics of each of the types that comprise the whole group. This may be of considerable interest to the younger pathologist who must rely largely on patterns for his histological diagnosis. It may also be of value to the clinician, since the natural course of a disease as well as its treatment will largely depend on the particular type of disease that is giving rise to the cirrhosis. The cirrhosis is simply a histological expression of an advanced stage of the disease that produced it, and, as one would expect, the pattern of each type of biliary cirrhosis will depend on the character of the particular disease that precedes it.

Originally the term biliary cirrhosis was used in a very restricted sense, and because there is still a certain amount of confusion about the use of this term today, a very brief historical sketch of the manner in which it has acquired its present usage may be in order. The term biliary cirrhosis appears to have been first introduced into the French literature by Nicati and Richaud, in 1880. Four years earlier Hanot had described a form of hypertrophic cirrhosis associated with jaundice which he distinguished from the commoner form of cirrhosis described about 60 years earlier by Laennec. Nicati and Richaud used this term of biliary cirrhosis to designate a pattern seen within the liver following prolonged obstruction to the common bile duct. As more cases of Hanot's hypertrophic cirrhosis were examined at autopsy, chronic obstruction of the common duct became an increasingly common finding. Experimental ligation of the common duct by a number of investigators at about this time produced a similar lesion within the liver, and Hanot conceded that the disease he had first described probably fell into this large group of obstructive cirrhosis. However, it must be admitted that an obstruction was not always found in all of these cases that came to autopsy. Be that as it may, the terms biliary cirrhosis and Hanot's cirrhosis for some time became practically synonymous.

Soon, as bacteriology developed and became increasingly important in the field of medicine, doubt was cast on the prevailing concept of simple obstruction being the cause of biliary cirrhosis. This was not only because of the intensity of the inflammatory reaction in the liver that was sometimes found but also because bacteria were often cultured from this organ and oc-

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* For references, see MacMahon, H. E.: Biliary Cirrhosis, *Lab. Invest.* 4:243-261, 1955.

casionally demonstrated in sections prepared from the livers of patients showing this disease.

In this country, after the turn of the present century, Mallory was probably the foremost investigator in this particular field of pathology, and at that time he would not recognize the term biliary cirrhosis, as it failed to convey to him a clearly defined entity; moreover, he did not believe that obstruction alone would cause cirrhosis. Influenced no doubt by the prevailing bacteriological concept of the etiology of inflammatory diseases, he coined the term in 1911 "infectious cirrhosis" to describe the late changes in the liver associated with inflammation within the intrahepatic system of bile ducts. In brief, he was introducing a new term for biliary cirrhosis. In passing, it is of some interest now to look back on that important paper, for in attempting to describe the early stages of this disease, Mallory made use of two livers from children. Each of these was the seat of an inflammatory reaction within the lumina of large, hyperplastic tortuous supernumerary dilated bile ducts. He did not realize then that he was describing an infectious inflammatory reaction in two livers that were already the seat of what is now recognized to be one of the commonest congenital malformations of the intrahepatic system of bile ducts. However, later in this paper, which has since become a medical classic, he clearly described a form of infectious cholangiolitis or cholangiohepatitis that led to a well-established and now accepted form of cirrhosis. This he called "infectious cirrhosis." Years later, as the result of work done in his own laboratory, Mallory did come to recognize simple obstruction as a cause of cirrhosis and clearly distinguished this disease from his "infectious cirrhosis," which he had described years before. During this later period Mallory pointed out that there is a mixed form, too, in which chronic infection may follow chronic obstruction or, in other words, a form of cirrhosis in which obstruction and infection may be combined.

If one is willing to concede the existence of "obstructive cirrhosis" and "infectious cirrhosis" and combinations of these two, there seemed to most pathologists to be no need for the use of the term "biliary cirrhosis" to designate this small group of diseases of the liver. Still there persisted in the minds of many clinicians and some pathologists the possibility of there being still a third disease belonging in this same category. Some of our standard textbooks, for example, continued to refer to Hanot's cirrhosis as something very distinct in itself, though reference to Hanot's original papers cast very little light on this subject. Most pathologists were inclined to believe that the disease originally described by Hanot was either "obstructive cirrhosis" or "infectious cirrhosis" or simply the fatty stage of Laennec's cirrhosis, associated as it so often is with jaundice. Such was our thinking, at least in this community, 30 years ago.

In 1938, just 20 years ago, this problem was again rekindled. Thannhauser and Magendantz had just introduced the term "xanthomatous biliary cirrhosis" to describe another form of biliary cirrhosis and also to designate a clinical syndrome. The cirrhosis was presumably associated with and initiated by xanthomatous deposits along the biliary tract within the liver. The syndrome was characterized by an enlarged liver, chronic jaundice, hypercholesteremia, and extensive cutaneous xanthomatosis. This new term, "xanthomatous biliary cirrhosis," was confusing to most pathologists because very few, if any, had seen it, whereas the clinical syndrome bearing the same name was being diagnosed more frequently over the country.

At this time, through Dr. Thannhauser, I was given the opportunity to study biopsy and autopsy material from cases belonging to this classical syndrome. What was found in the livers of these patients was not a deposition of xanthoma cells within the

portal areas as we had suspected but rather a nonspecific chronic proliferative inflammatory reaction in almost all of the portal areas. This pattern was distinctly different from that of simple obstructive cirrhosis, and it could also be distinguished from the pattern of "infectious cirrhosis" as described by Mallory. There were, however, certain features in common with each of these two accepted types. Knowing nothing of the etiology of this new form of cirrhosis and recognizing that it could occur in the absence of xanthomatosis, it seemed best to designate it by a simple descriptive term that would distinguish it from the other two types already described. So it was that the term "pericholangiolitic cirrhosis" was first used, in 1948. In this disease a low-grade chronic insidious inflammatory reaction, concentrated around the cholangioles, led to fibrosis of the portal areas and a striking disappearance of interlobular bile ducts. The extrahepatic biliary tract was consistently free of disease.

If my reader has followed me to this point, it will now be apparent that there were three diseases of the liver having a very similar pattern, namely, "obstructive cirrhosis," "infectious cirrhosis," and "pericholangiolitic cirrhosis." It seemed convenient and proper to group these three conditions because of their similar pattern within the liver, and "biliary cirrhosis" was the most suitable term for this group. In the course of recent years, still other types showing similar patterns have been added to this group. Today at least seven patterns representing seven distinct diseases may be included.

The common denominator of this group of diseases may be characterized by an increase in width of the portal areas as they spread out from the hilus into the substance of the liver. There is a variable degree of bile stasis, and for a long time at least the normal lobular pattern is preserved. So much for the histology. As for the gross, there is usually a moderate increase in weight and size of the liver. Its surface at first smooth, may acquire a fine granularity or cobbling, and as the disease progresses the consistence will be altered. The color will vary, depending largely on the degree of congestion and on whether or not cholestasis is present at the time of examination. Except in far-advanced cases, the gross findings in biliary cirrhosis are usually minimal compared with those of long-standing Laennec's or pigment cirrhosis or postnecrotic cirrhosis or even the cirrhosis of long-standing congestive failure. The increase in size of the liver is the result of an increase in width of the portal areas, and this in turn is the result in large measure of a chronic inflammatory reaction. The character of this reaction, its duration, its exact location, and its etiology will vary from case to case, and it is these four variables that play such an imporant role in determining the individual characteristics of the several types that comprise the entire group. Jaundice is a common finding, but bile stasis is not consistently present. Portal hypertension is rarely serious, and the so-called signs of liver failure in this group of diseases are rarely encountered.

Before describing each type individually, a word of warning to the pathologist may be in order, for we are dealing here with a group of diseases whose histology is constantly changing, and for this reason a single cross sectional description of any one type affords a very inadequate picture of the entire disease process. There is, however, for each type a fairly characteristic pattern. In the early stages this will not be fully established, whereas in the late period the very pattern upon which a specific diagnosis was possible may be completely altered. In such cases, without recourse to earlier biopsy material from the same patient, a histological diagnosis in the end-stage of a disease process may be very uncertain. There are bound to be borderline cases; there will be mixed cases, and there will be still others belonging to the group that will defy further classification.

1. Obstructive Biliary Cirrhosis

The commonest and best known type of biliary cirrhosis is that seen following uncomplicated long-standing extrahepatic bile stasis. The earliest histological changes are characterized by a variable degree of centrolobular bile stasis, a mild inflammatory reaction in each portal area, a dilatation and a modest proliferation of cholangioles, and, finally, a moderate increase in connective tissue. This picture may be complicated by necrosis of small patches of liver cells, a spillage of bile into the parenchyma, and even inspissation of bile casts in collecting ducts with the formation of intrahepatic concretions. If the obstruction can be removed, the disease is arrested and recovery with good anatomical and functional restitution is the rule.

2. Cholangiolitic Biliary Cirrhosis

In this disease there is an active inflammatory reaction within the lumen and walls of the cholangioles. The pattern, however, is dominated by an inflammatory hyperplasia of cholangioles together with a moderately rich leukocytic infiltration into the portal areas. Bile stasis may or may not be a feature. The disease does not involve all portal areas uniformly, and in any one portal area it is usually very asymmetrical as it spreads out to encroach upon the bordering lobule. As granulation tissue matures, scar tissue forms, and this may obliterate bile ducts and veins in the portal areas. Though originally thought to be exclusively bacterial in origin, viruses, toxoplasma, drugs, allergy, and possibly autoimmune mechanisms have been added as etiological factors. This disease may be accompanied by inflammation in the large bile ducts, and a similar disease may appear simultaneously within the pancreas. If the cause can be found and eliminated, the disease is basically benign, though considerable scarring with some reconstruction is common.

3. Pericholangiolitic Biliary Cirrhosis

This is seen much less commonly than the two that have just been described and seems to favor particularly middle-aged women. The underlying disease is an insidious chronic granulomatous inflammatory reaction in each of the portal areas, and lymphocytes dominate the cellular infiltration. The first changes to appear are seen at the junction of the liver cells and portal areas, where there is a mild inflammatory reaction about the cholangioles. It spreads along the sinusoids and into the perisinusoidal spaces as it encroaches on and destroys the periphery of the lobule. Perhaps the most important change is a progressive disappearance in the interlobular bile ducts, and portal veins too may disappear in this inflammatory reaction. Bile stasis is most conspicuous at the periphery of the lobules. In the beginning, this disease is only recognizable under the microscope, but it may progress for years, leading to hypertrophy, nodularity, and diffuse scarring. The etiology is still unsettled, but chemicals, allergy, and, most recently, autoimmunization are most favored. In passing it may be pointed out that this particular disease has been the one most frequently encountered in cases of severe biliary hypercholesteremic xanthomatosis. In the end this disease may terminate with complications of portal hypertension or liver failure, since it tends to run a progressive course.

4. Acholangic Biliary Cirrhosis

This is a disease of infants and children. In contrast to the "obstructive type of biliary cirrhosis," that is not infrequently found in this early age group, simply as the result of congenital stenosis or atresia of the common bile duct, acholangic biliary cirrhosis is associated with a congenital defect in the growth and development of the intrahepatic interlobular system of collecting bile ducts. This latter condition may be found in the presence of an extrahepatic biliary system that is (*a*) normally de-

veloped, (*b*) rudimentary, or (*c*) absent. In the presence of an intact and orderly extrahepatic bile duct system, this intrahepatic defect can be easily overlooked in one's diagnosis. The histological pattern may vary from case to case, but assuming that the extrahepatic system of ducts is intact, the changes in the liver are fairly constant. Moreover, the prognosis in this group with an intact extrahepatic free flow of bile is reasonably good, since there is now evidence to show that in the course of time, with the continuous growth of the liver, children may outgrow this initial anomaly. Needless to say, in its extreme form, with complete intrahepatic agenesis of the collecting ducts, the disease usually terminates fatally within the first year.

The liver is somewhat enlarged, icteric, and smooth, with little or no detectable change in consistence. Histologically, in addition to the diminution or absence of a collecting system of interlobular ducts, there is a minimal chronic inflammatory reaction in most of the portal areas. Though the perilobular cholangioles — embryologically derived from the liver cells—are usually inconspicuous, they may show a moderate proliferation. Bile stasis in both canaliculi and perilobular cholangioles is obvious. The liver cells themselves may be little affected; occasionally they group themselves into tubules; at other times some may become grotesquely large and contain many nuclei—a change that may mimic one seen in viral infections and also in other forms of bile stasis. In chronic cases jaundice may be associated with hypercholesteremia and widespread xanthomatosis.

5. Fibroxanthomatous Biliary Cirrhosis

In my experience this has been a very uncommon entity confined to very young children. The disease responsible for this form of biliary cirrhosis is a primary diffuse xanthomatous reticuloendotheliosis that may involve almost every organ in the body. Of particular interest at this time are the changes that may be confined to the portal areas in the liver. Each of these areas is widened and lengthened by a solid proliferation of histiocytes, some laden with lipid, and connective tissue. This growth of cells encroaches upon and obliterates the interlobular bile ducts, and, as the disease advances, these proliferating cells creep over into the peripheral zones of the bordering lobules. These changes lead to bile stasis, an increase in size of the liver, and a definite change in consistency. A modest infiltration with lymphocytes generally accompanies this proliferating process. The blood cholesterol, usually normal during the early stages of the disease, may increase slightly as biliary obstruction becomes more manifest. The disease is progressive.

6. Biliary Cirrhosis Associated with Cystic Fibrosis of the Pancreas

In a small number of infants and children with cystic fibrosis of the pancreas, the liver will be diffusely scarred and the surface of the liver may resemble that of the kidney in cases of old healed pyelonephritis. Here there is a widening of the portal areas as the result of a mild chronic inflammatory reaction bordering a proliferation of cholangioles that are distended with basophilic mucus, eosinophilic debris, and inspissated pools of bile. The bordering liver parenchyma is well preserved, though giant multincleated cells are occasionally encountered. Bile stasis within the lobule may be conspicuously absent. The most characteristic feature of this type of cirrhosis is the stasis and accumulation of mucus and bile within the intrahepatic biliary tract in the absence of any form of intra- or extrahepatic mechanical obstruction. Clinical manifestations of this form of cirrhosis are generally negigible, and it is usually at the autopsy table that this disease of the liver is first encountered.

7. Carcinomatous Biliary Cirrhosis

This is one form of biliary cirrhosis that has to be seen to be believed. The underlying disease is a metastatic carcinoma

growing throughout the lymphatics of all of the portal areas. The presence of these tumor cells initiates a chronic inflammatory reaction in each of the portal areas. This leads to a widening of the portal areas, to bile stasis, and to cirrhosis. In the one case that I have seen at the autopsy table, the liver was enlarged, finely granular, deeply jaundiced, and very diffusely scarred. A diagnosis of malignancy was not entertained in the gross. Only histological studies revealed the true nature of the disease, which had begun as an infiltrating carcinoma of one breast months before. Of equal interest in this case was the almost paradoxical fact that the liver was the only organ significantly involved in the metastasis.

Comment

This classification of biliary cirrhosis has purposefully omitted the term "Hanot's hypertrophic cirrhosis," not to discredit Hanot for significant contributions that he made in the field of liver pathology in the last century but rather because it would now appear that the "hypertrophic cirrhosis with jaundice," which he did describe grossly, included several different diseases rather than a single specific entity. Another term that has recently gained popular usage, namely, "primary biliary cirrhosis," has also been avoided, since this term, first introduced years ago, has come to imply different things to different people. Moreover, it does not describe a lesion and hence has little place in a classification based on histological patterns.

As for the term "biliary cirrhosis" itself, there are those who believe that medicine would be better off today if this term could be forgotten. Some of these people would also erase the word "cirrhosis" entirely, since it is nothing more than an advanced stage with scarring of a number of entirely different diseases of the liver. Be that as it may, grouping is still popular in medicine, and collective terms are commonly found in relation to diseases involving almost every organ in the body. Within limitations these serve a very useful purpose, but collective terms become of even greater value when one is aware of the number of distinct and separate diseases that may comprise them. Biliary cirrhosis is such an example. Originally it implied a single disease; later, two; still later, three, and today it comprises at least seven and possibly more separate entities. These include "obstructive biliary cirrhosis," "cholangiolitic biliary cirrhosis," "pericholangiolitic biliary cirrhosis," "acholangic biliary cirrhosis," "fibroxanthomatous biliary cirrhosis," biliary cirrhosis in cystic fibrosis of the pancreas," and, lastly, "carcinomatous biliary cirrhosis." In each of these there is a chronic inflammatory reaction with scarring in the portal areas.

This list does not include the so-called pseudocirrhoses associated with leukemias and Hodgkin's disease or the congenital cystic dysplasias of the intrahepatic bile ducts so often associated with cysts of the liver and kidney and with anomalies in the portal circulation; nor does it include the occasional case of allergic vasculitis or sarcoidosis centered in the portal areas. Lastly, it does not include the isolated case of fibrosis in the portal areas associated with a deposition of Thorotrast. These are lesions that only mimic the pattern of biliary cirrhosis.

Books

EDITED BY WILLIAM B. BEAN, M.D.*

Recurrent Maladies in Scholarly Writing. By Eugene S. McCartney, Ph.D. Price, $2.50. Pp. 141, with illustrations. University of Michigan Press, Ann Arbor, Mich., 1955.

Guide to Medical Writing. By Henry A. Davidson, M.D. Price, $5. Pp. 338, with illustrations. Ronald Press Company, 15 E. 26th St., New York 10, 1957.

Rx for Medical Writing. By Edwin P. Jordan, M.D., and Willard C. Shepard. Price, not given. Pp. 112, with illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1953.

Voices of criticism crying in the wilderness against empty words and sterile style are a traditional occupational tic of editors and critics. There are many examples of this, and one certainly appropriate to medical writing today is a quotation from Matthew Arnold's Preface to the 1853 edition of his poems, in which there is the following statement:

> "The confusion of the present times is great, the multitude of voices counselling different things bewildering, the number of existing works capable of attracting a young writer's attention and of becoming his models, immense: what he wants is a hand to guide him through the confusion, a voice to prescribe to him the aim which he should keep in view, and to explain to him that the value of the literary works which offer themselves to his attention is relative to their power of helping him forward on his road towards this aim. Such a guide the English writer at the present day will nowhere find. Failing this, all that can be looked for, all indeed that can be desired, is, that his attention should be fixed on excellent models; that he may reproduce, at any rate, something of their excellence, by penetrating himself with their works and by catching their spirit, if he cannot be taught to produce what is excellent independently. Foremost among these models for the English writer stands Shakespeare."

These are sage words for anyone today who is writing medical and scientific reports and who wishes to develop a distinctive style of his own. But even before he writes with grace and elegance, before his enthusiasm can be transmuted into eloquence, he has got to know the rules of the game and stick by them. Whether the present low ebb of writings in medicine and science has resulted from the decay of interest and training in the Classics and the Humanities is not for me to say, but the sequence at least admits that possibility. It is too late to reform the education of those who are now writing papers, if, indeed, one should use the term "education" to describe any of their past experience in prose composition.

Great failures of our modern systems of education are revealed in what the modern age refers to in the uncouth word communication. We see examples in almost any issue of any medical or scientific journal we choose to read. Despite much writing about writing, there is no happy gradual trend toward consistent improvement. Even formal societies dedicated to improving writing and medical "literature" often have in their journals messages which display flagrant examples of that which they inveigh against. I have addressed myself to this problem of poor writing and poor delivery of reports in several papers. Though I can attest to the widespread interest in much that has been written about medical writing, I see no progress. The movement is consistently erratic. The three books I am reviewing now, all written on the basis of much and varied experience, have in common a singularly light style. In fact, they are written almost in a merry tone, as though nothing ever really could be done to improve the writing of that already vast and still growing horde of persons who feel constrained to put into print papers dealing with medical problems, patients, and research. This plight is epitomized in a series of questions by McCartney. "In our frantic zeal to extend the frontiers of knowledge are we not neglecting to learn how to make workmanlike records of what we find?

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Are we not undertaking distant explorations without having first provided some essential equipment? Is it not a tragedy when the enterprise, the resourcefulness, and the determination shown in the conduct of a long, perhaps extremely costly, investigation are not continued into the reporting of it? Is not a critical reader warranted in being somewhat mistrustful of accuracy of findings that are hastily and shabbily presented? Is a research product satisfactorily completed before the results are made available in adequate form?" Elsewhere McCartney, from the rich resources of a lifetime spent in editing and working for one of the university presses, discusses other parts of problem in chapters with such charming names as "The Studied Avoidance of Simplicity," "Saying it with Flowers," "Is Scholarship Always Scholarly?" "Some Participles I have Met," "The Tautological Phrase of Specification," "Oddities in Measuring and Counting," and "Illogicality." In essence he approaches the problem from the point of view of the pathologist, dissecting out all the necrotic absurdities of style, chronic passive congestions of obscurity, and the neoplastic excrescences of redundancy with their metastases which lead to certain death. His is a scholarly book for scholars, full of delightful quotations as well as a scandalous collection of errors he has run into. His view is that of the faintly cynical pathologist, with a fatalistic shrug from long years of labor in the dead house but with the saving grace of a chuckle or at least a wink.

Davidson's book, written with a smile, almost a laugh, is a practical and straightforward essay. He has fun with the tactics of syntax, stalking the idea, how to hook the reader, how to hook reader interest, certain rules of nomenclature, the admonition to write not telegraph case histories, and some strictures on work choice. There is much practical advice along with many lists of drugs, treatments, and especially eponyms, which he is against. I am far from agreeing with him that we can always dispense with eponyms, however bothersome and misapplied they may be. For instance, hemangiomatosis is certainly not the same thing as Hippel-Landau disease. But Davidson's cheerful book is packed with good sense, running the gamut from how to find the inspiration which is supposed to get an article started through the galleys to final publication. The approach by Davidson is that of the clinician with all sorts of helpful suggestions. He is a physician to the writer. Because of its practical value, this book should be very helpful to anyone who takes the trouble to follow its advice. It, too, is a pleasure to read and a helpful study.

The book by Jordan and Shepard deals with the practical therapeutics of medical writing. It lives up to its title well. It is short, concise, and to the point. It includes a great many practical matters, such as making an index, the various stages in reviewing, criticism by an author of his own work, employment of statistics, making graphs, handling photographic material, and many suggestions which should be helpful not only in preparing the average short paper but particularly in writing a monograph or book. It is too short to be as useful as the others for reference. It is straight therapy to be taken whole.

Each of these books serves a different need, and all three are to be recommended heartily to those who wish to improve their writing. Unless, however, writers make some effort to follow the instructions consistently and become their own tutors, it is unlikely that reading these potentially most helpful books will be of any value. There is a spate of such books already. Even with a further proliferation of guide books like these, current writing declines in quality, though it increases by leaps and bounds in its mass, forming a truly "monstrous regiment" of medical papers which come flooding forth from the presses with abundant and increasing vigor. As I have said elsewhere, Pandora's box probably contained a printing press.

WILLIAM B. BEAN, M.D.

At Doctor Mac's. By Peter Quince. Price, 15 s. net. Pp. 277. J. M. Dent & Sons, Ltd., Publishers, Aldine House, 10 Bedford Street London, W. C. 2, 1958.

Tuberculosis and the busy beehive of the sanatorium life of the tuberculous provided the theme of one of the great books about medicine, Thomas Mann's "The Magic Mountain." Peter Quince's most recent book, "At Doctor Mac's," with the subtitle "A Documentary Entertainment," certainly will be compared with "The Magic Mountain" and in most respects very favorably. It may be looked upon as the biography of an institution. Its scope embraces three levels of organization: the organic life of an institution, in this case a sanatorium; the people who are sick and thus reluctant guests, and those who minister unto them. The feelings and sensations of a person with a chronic disease like tuberculosis are described vividly for us and are embodied clinically in the different characters, each of whom is drawn with a strong sense of reality. There is another set of intertwining lives, those of the physicians, nurses, and their army of assistants who run the hospital and care for the patients. These

three lives, the hospital, the patient, and the medical person, work out the pattern of their mingled destinies in a superbly written book which holds our attention from beginning to end. My own interest may be unusually deep, since I have had the pleasure of visiting the sanatorium which is the scene of the story and thus have a scaffolding on which to build my mental picture. Despite what the author disclaims in stating that the characters and incidents in the book are fictitious, they have emerged from a long and fruitful as well as intensely perceptive experience in a tuberculosis sanatorium during the days before state medicine came to Great Britain. Elegant medical aphorisms are scattered through the book in a way which should make it especially useful for the undergraduate student or the person considering medicine as a life work.

Dr. McClellan, the chief of the sanatorium, is philosopher, guide, and friend, slipping casually again and again into a semirecumbent position as he leans back in a chair in a patient's room or in his office to fall into philosophic reverie and discourse. The philosophy of Dr. McClellan is developed as a consistent and humane view of the world and of sick people, to whom he brings the long training of general practice, a deep sensitivity to psychoanalytic constructs, a sympathetic understanding of Groddeck, a philosophic and ecological view of tuberculosis, and most of all a love of people with just enough paternal feeling to keep it fresh and wholesome. There are especially thoughtful comments on why certain people get tuberculosis and others do not, why some fare much better with the disease and go on to prompt recovery, while others, less seriously ill at the start, decline and die. We find the attention concentrated on the person who harbors the illness rather than the germ or the disease itself. One refreshing aspect is a thoroughly critical and skeptical view about chemotherapeutic agents as anything more than crutches, useful, but still crutches, in dealing with tuberculosis. All these and many more ideas are set forth with skill. There is just enough plot to keep things moving along and never to much to keep us from following the intimate interweaving of the lives of sanatorium, patients, and staff. Perhaps medicine has made very real strides, for we do not feel the same hostility between patient and physician which was so apparent in "The Magic Mountain." There is more warmth and more understanding, as though the spirit of the sanatorium were telling the tale. The emphasis is on the person and the personality of the patient as well as the tubercle bacillus and their deep inter-relations, which have had such profound effects on history and made such a large mark on literature and other forms of art.

For those who have continued to take a sour view of doctors and modern medicine as dispassionate, scientific, hard, and impersonal, this book, though its scene is in England, should make even the most skeptical layman realize that there are many splendid physicians and institutions where humane care and love may be blended with a high degree of scientific precision and up-to-date therapy. Such a coming together is told in this book with wisdom and delight.

WILLIAM B. BEAN, M.D.

The Medical Management of Cancer. By Henry D. Diamond, M.D., F.A.C.P. Price, not given. Pp. 179, with 23 tables, 40 figures, and 13 charts. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1958.

The subject material in this well-documented text is based on and presented from considerable personal experience by the author from his work at the Memorial Center for Cancer and Allied Diseases, New York. The foreword endorsement by Lloyd F. Cramer, M.D., adds prestige.

This monograph is divided into two sections and an appendix. The first section deals with cancers where the primary treatment is medical (nonsurgical); this first section covers the malignant lymphomas, the leukemias, and plasma-cell myeloma. The second section discusses the medical management where the primary treatment is surgical—neuroblastoma, cancer of the lung, thyroid, ovary, breast, and prostate. A final section, or appendix, reviews the literature and presents the experience at the Memorial Center on the intracavity use of injectable radioisotopes. The appendix was edited by the author but was prepared by Richard Y. Card, M.D., and Ulrich K. Henschke, M.D. The index and bibliography are satisfactory. The illustrations have been selected carefully.

Each entity is covered systematically, through pathology and natural history, diagnosis and pathologic physiology, treatment, and end-results. The coverage on some surgical diseases (second section) is brief, probably necessarily so, but the first section is very well done. At times referrals to charts and tables are confusing. Also, on page 16 the clinical classification of the malignant lymphomas might be weighted more heavily for use in immediate referral and included in the index.

This monograph is well worth while. It has been directed toward the internist, but the medical student and the surgeon will enjoy and appreciate the book. It is, as stated by Dr. Cramer, a valuable source of reference and orientation.

ROBERT C. HICKEY, M.D.

Frontiers of Knowledge in the Study of Man. Edited by Lynn White Jr. Price, $4.50. Pp. 330. Harper & Brothers, 49 E. 33d St., New York 16, 1956.

Lynn White, for a long time President of Mills College and now teaching history and the humanities at Stanford University, once wrote a very wise book entitled "The Education of our Daughters." In it he pointed out that the education of women in the United States today was badly neglected. It was one-sided, missing its absolutely essential double theme and purpose. The life of the American woman, except for a few career girls and spinsters by design or fate has been that of a mother in the home raising a family. Though this is more than a full-time job, it has finite temporal dimensions. When it ends, far too many women who have done well enough as mothers suddenly are thrown on their own resources when the fledglings leave the nest. Then suddenly some women may find that their resources are small indeed. Lack of training for the personal life of and on their own, or for a career in their mature lives, often reveals poor aptitude for the second career. Many women then wander around in aimless confusion, wasting time because of undeveloped talents and capacities. This book, suggesting an educational remedy, was so interesting that I was anxious to see what Lynn White had gathered together as editor of this later book, one purporting to deal with the frontiers of knowledge. We all know now that these frontiers are in a constant state of flux and movement. This is a fine book, as we see at once from the contributors and the topics; though any physician may be somewhat peeved that medicine and biology were omitted from consideration in "Frontiers of Knowledge." This oversight may result from the ignorance of the editor, oversight, or his inability to find someone he thought a competent spokesman. In any event, here are collected not only some details of the impact of science and all its new ideas, techniques, and apparatus upon the life we live but also a thoughtful analysis of our culture. This is considered from the point of view of anthropology, archeology, art, economics, genetics, geography, history, and the history of science, linguistics, literature, mathematics, musicology, philosophy, politics, psychology, religion, and sociology, with an excellent summing up by the editor of the changing canons of our culture. While this book illustrates the fragmentation of knowledge, it also is an example of one of the ways in which this great mosaic of broken shards can be fit together in a congruent and enlightening as well as esthetically appealing unity, a unity not quite complete because of the omission of medicine and biology.

WILLIAM B. BEAN, M.D.

Angiographie der Nieren. By Erich Vogler and Rudolph Herbst. Price, $12.85. Pp. 112, with 182 illustrations. Georg Thieme Verlag, Herdweg 63 (14a), Stuttgart N, 1958.

Angiographie der Nieren, by Erich Vogler and Rudolph Herbst, is the result of the collaboration of a radiologist and a urologist in the performance of five hundred arteriograms. This small but excellent volume presents the subject in a very thorough manner and shows the results of great experience and the development of precision techniques.

The authors employ special x-ray equipment which permits exposures of one-tenth to one-twenty-fifth of a second, and automatic cassette changers which make it possible to take twelve to fourteen exposures at one-half-second intervals. This makes it possible to demonstrate the circulation of the radiopaque medium in its arterial, intermediate, and venous phases and greatly enhances the diagnostic possibilities of the method.

The authors employ a special cannula which permits easy penetration of the aortic lumen without the danger of perforation of the opposite wall.

The illustrations are superb. This is the finest monograph upon the subject which I have seen.

FREDERICK A. LLOYD, M.D.

Rehabilitation of the Cardiovascular Patient. By Paul Dudley White, M. D.; Howard A. Rusk, M.D.; Philip R. Lee, M.D., and Bryan Williams, M.D. Price, $7. Pp. 176. The Blakiston Company (division of McGraw-Hill Book Company, Inc.), 330 W. 42d St., New York 36, 1958.

On rare occasions a book may be judged by its cover. This is one of those occasions. One would expect on seeing the title and the authors that the contents would be erudite, informative, factual and well presented. After reading the volume, I was not disappointed.

The book has an unusual foreward by Mrs. Mary D. Lasker in which much of the philosophy of rehabilitation is epitomized in terms of both human factors and economic burden to the nation. The chapter on historical development of rehabilitation is most unusual and interesting. The various chapters of the text are well delineated, i. e., cerebrovascular disease, rheumatic fever, and rheumatic heart disease; congenital heart disease; hypertension and coronary heart disease. Each chapter states the attendant problems incurred with each form of cardiovascular disease and summarizes the experience of the authors and others in the field of cardiovascular rehabilitation. There are numerous sentences which are worth quoting, for they exemplify the practical as well as the cogent thinking which has gone into this monograph, e. g., "In each case, the program should be designed to meet the needs of a specific patient and should not be merely the application of a standarized routine." On page 126, "When the physician evaluates the social and vocational status of a cardiac patient, it should be with the knowledge that the great majority are able to live relatively normal productive lives."

Rehabilitation has often been referred to as the third phase of medical care. The era in which we are living will produce even greater numbers of cardiac patients, and hence the third phase of medical care will become of prime importance. The physician of the future and those in active practice today must face this fact and learn that only by assessing the medical, surgical, vocational, social, and environmental factors of each patient will he be in a position to advise each patient how "to live within the limits of his disability but to the hilt of his capabilities." This monograph is recommended for all those physicians who are interested in learning the problems, fundamentals, and philosophy of the type of medicine which will be of prime importance in the near future.

M. GERTLER, M.D.

Sherrington, Physiologist, Philosopher, and Poet. By Lord Cohen of Birkenhead, M.D., D.Sc., LL.D., F.R.C.P., F.A.C.P., F.F.R., F.S.A., J.P., Professor of Medicine. Price, not given. Pp. 108, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

The fourth of the Sherrington Lectures deals with Sherrington himself. It is a warm but critical appraisal of Sherrington which throws light not only on the subject but on the author. For those who have received stimulus from Sherrington's work and from his writings, this sketch is very rewarding, even though at times the critic tends to be perhaps overcritical in his attitude. I can remember a half dozen books which made an abiding impression on me when I was an undergraduate medical student or since. Sherrington's "Integrated Action of the Nervous System" leads the list. In this book I came face to face with a man who combined a marvelous intellect, great technical skill, imagination, and the capacity to describe his work in a pleasing and felicitous style which few physicians have equalled and hardly anyone has surpassed. Then later, in a more philosophical frame of mind, his "Ordeal of Jean Fernel" and "Man on His Nature," as well as his modest autobiographical sketch in "Scientific Medicine and History: Essays in Honor of Charles Singer," have increased my pleasure. Fernel has remained a favorite. Most of the critical part of Cohen's lectures deals with Sherrington's employment of the Cartesian mind-brain dualism. Since this is not a topic which lends itself to scientific exposition, indeed it is one which can never be solved by argument, my feeling is that Sherrington has stated his case much better than Cohen, though others no doubt will not agree.

The last essay in the book, "Sherrington as Poet and Philosopher," the third of three lectures, appeals to me most. Despite the sometimes astringent tone of the author's views, Sherrington emerges as a man of Elizabethan quality in whom there was a happy mixture of scientist, poet, philosopher, and at times a mystic. For those who wish a model of lyrical prose, his "Jean Fernel" and "Man on His Nature" are examples most could copy with great profit, and it would be to their benefit to get to know Sherrington and Fernel better. Both were remarkable physicians, physiologists, teachers, and writers. Cohen has done us a service in calling them so vividly to our attention.

WILLIAM B. BEAN, M.D.

The Preservation of Youth. By Moses Maimonides. Introduction by Hirsch L. Gordon, M.D., Ph.D., D.H.L. Price, not given. Pp. 92. Philosophical Library, Inc., 15 E. 40th St. New York 16, 1958.

Maimonides is high in the ranks of physicians who helped bring to Europe some of Greek medical tradition by way of Arabic sources. A twelfth-century Jewish physician, he was

distinguished as a court physician in Egypt and as philosopher, critic, and commentator. He had a keen historical sense and very high ideals of medicine. This book is actually a letter he sent to the sultan. It contains a great miscellany of advice—some sage, some curious, some we would now consider sheer quackery—but in many ways it is strikingly modern and up to date, considering its age of eight hundred years. Maimonides advises against eating much food in hot weather, praises exercise which he says removes the harm caused by most bad habits which most people have, extols the virtue of well-prepared whole wheat bread and scorns bread made of refined flour, and urges the avoidance of fat. He has some wise views on preserving health and preventing disease instead of just treating illness. He has some hints about ecology and the relationship of environment to disease and health but is not above the usual rigamarole about aphrodisiacs, though he is not enthusiastic about them. His psychosomatic philosophy is presented in strikingly contemporary words. Throughout he advises optimism. He ends one chapter with the sage statement, "This is all that your servant felt is needed in this chapter," a point which most writers should be reminded of about half way along in any chapter or paper. He was especially anxious that nature not be interfered with. If a cure was not available, do not mess around. Maimonides seems to have taken a fairly dim view of sexual intercourse, perhaps because he wrote this book in his later years. Anyhow, I have doubts that this particular bit of advice was influential in providing the sultan and his harem with a modus operandi. Somehow the vivid but casual advice of Maimonides about preserving youth calls to mind the informal code attributed to Satchel Paige, that immortal Negro pitcher whose recipe for staying young includes these items:

"Avoid fried meats which angry up the blood. If your stomach disputes you, lie down and pacify it with cool thoughts. Keep the juices flowing by jangling around gently as you move. Go very lightly on the vices, such as carrying on in society; the social ramble isn't restful. Avoid running at all times. Don't look back. Something might be gaining on you."

WILLIAM B. BEAN, M.D.

Human Blood in New York City: A Study of Its Procurement, Distribution and Utilization. Conducted by the Committee of Public Health, the New York Academy of Medicine; Dr. H. D. Kruse, General Director of Study. Complimentary. Pp. 147. The New York Academy of Medicine, 2 E. 103d St., New York 29, 1958.

This publication presents statistical data pertinent to blood banking in a unique large metropolitan area along with recommendations for improving community blood banking services. It is primarily of interest to physicians directly concerned with blood banking.

FRANCIS J. TENCZAR JR., M.D.

Religious Doctrine and Medical Practice. By Richard Thomas Barton, M.D. Price, $3.75. Pp. 94. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

Sooner or later any practicing physician will find himself up against some special problems in a patient with unfamiliar religious beliefs. He wants a good, clear, but brief guide to the various rituals, requirements, practices, and customs of religions he is likely to run into, and Barton's book is very helpful in this respect. There is a particularly useful chapter on "Religions of Western Origin," which multiply without end. But there is enough on the others so one can get the necessary first-hand information. While a physician may feel that a patient is being pigheaded in refusing treatment which may save his life, the patient, along with the rest of suffering humanity, has personal rights. In our society these rights sometimes are directly and at other times obliquely suicidal but must be respected regardless of our personal views. This is a useful handbook for physicians, nurses, and hospital administrators as well as anyone else who has a part of his duty dealing with sick people. Though the meaning is generally intelligible, the book is not well written. One finds the word "pathology" used repeatedly where the reference is to lesions rather than the study of lesions. The author mentions "two first converts," though obviously there can be but one first in any given category. Despite these and other awkward usages, the book is a useful guide and well fulfills the purpose for which it was written.

WILLIAM B. BEAN, M.D.

A Therapy for Anxiety Tension Reactions. By Gerhard B. Haugen, M.D.; Henry H. Dixon, M.D.; Herman A. Dickel, M.D. Price, $3.50. Pp. 110. The Macmillan Company, 60 5th Ave., New York 11, 1958.

The Neuroses and Their Treatment. By Edward Podolsky, M.D. Price, $10. Pp. 555. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1958.

There are periods in the growth of science when it is well to turn our attention from the imposing superstructure and to examine the foundations. The foundation of science is the scientific method; the unity of the sciences reflects the method and not the material. Karl Pearson observed that the method of science is characterized by careful accurate observation, by classification of the data in sequence and correlation, by the recognition of scientific laws, by self-criticism, and by the final criterion of acceptance and confirmation by others.

The scope of science is to ascertain truth in every branch of knowledge. How does psychiatry measure to the rule of the scientific method? Descriptive psychiatry derives from correlated data; the clinical pattern can usually be fitted to a "disease" listed in the diagnostic manual of the American Psychiatric Association. Psychiatric research in biochemistry and physiology also reflects the methods of the natural sciences. Other branches of psychiatric endeavor often appear to be a mixture of unvalidated hypotheses with ingenious but obscure propositions, flavored with pure speculation, colored with jargon, half baked, and swallowed with fervor. One might expect our psychiatrist friends to suffer from inadequate digestion of this mixture, but a sprue-like syndrome is probably precluded by total uncritical absorption. There have been great advances in psychiatry in the last one hundred years: the opening of the locked doors, the development of the physical methods of therapy, the use of drugs, the recognition of the value of listening to the patient (although few internists can be so naïve as to think that this is a psychiatric invention), and the work of Sigmund Freud. It is difficult to measure the importance of Freud. We can look at psychiatry only from the standpoint of the past, and we are too close to our age, in time and in feeling, to appreciate without prejudice and without material foreshortening the magnitude of the changes in thought that Freud has stimulated. To appreciate him I think it is necessary to realize that Freudianism is not a school so much as a state of mind, and unless one is in key with that thinking—even if one does not understand it or indeed necessarily sympathize with it—Freudianism may seem incomprehensible. The history of medicine reveals many periods where the uncritical acceptance of some widely circulated dogma has stopped growth. The Freudians may have done psychiatry more harm than good, especially where wholesale acceptance has resulted in the exclusion of other considerations, in the ignoring of the principle of multiple causality, and, dare one mention it, in the exclusion of disciplinary and of spiritual values in our considerations of etiology and of treatment. It is of consequence that a man should not be condemned because of his followers. I am so conscious of the ease of criticism and of the difficulty of reconstruction that I will not stop short at the lighter task. There is a vast gap in the study of the natural history of the neuroses and of the controlled assessment of the results of treatment by psychotherapy. Psychiatry needs those who pursue the methods of science, the skeptic who is aware of the dangers of speculation, the rules of logic, the objective method, the statistical control, and one who does not under-rate the duty of thinking. To state hypotheses and devise suitable experiments may be formidable but is not insurmountable.

"A Therapy for Anxiety Tension Reactions" describes a simple way of treating one of the commonest illness of our time. The method is to teach patients how to relax. The authors, professors of psychiatry at the University of Oregon, rarely treat their patients for more than twenty minutes at a time; they usually complete their course of treatment in two months, and they specifically tell their patients that there is no magic relief to be gained by the patient's recounting his personal life. The test is explicit, direct, practical, and free of jargon. The whole book is fresh and stimulating, although the prose is set at a Dale Carnegie level and the authors hoist themselves on their own petard by giving no figures of the results of their treatment. Nevertheless, it is a pleasure to award my personal annual prize to the authors, for, though psychiatrists, they have written only one page on sex, and this to decry its importance. This book should be required reading for psychiatrists, and I enthusiastically recommend it to all busy physicians who think that current psychiatry is a lot of malarkey but who are trying to treat sick patients.

"The Neuroses and Their Treatment" is an unfortunate chiaroscuro of modern psychiatric thought. It contains thirty-eight representative papers. There are excellent sections by Holmes on experimental studies in anxiety reactions, and by Miles and others on the evaluation of psychotherapy. Much of the rest is regrettable guesswork or nonsense.

Medicine as a whole has made its greatest advances through the application of the scientific method. "Even mistaken hypotheses are of use in leading to discoveries. . . . It seems indeed a necessary weakness of our mind to be able to reach truth only across a multitude of errors and obstacles," wrote Claude Bernard; also ". . . it is better to know nothing than to keep in mind fixed ideas based on theories whose confirmation we constantly seek, neglecting meanwhile everything that fails to agree with them." Bacon wrote, "if a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties."

DANIEL B. STONE, M.D.

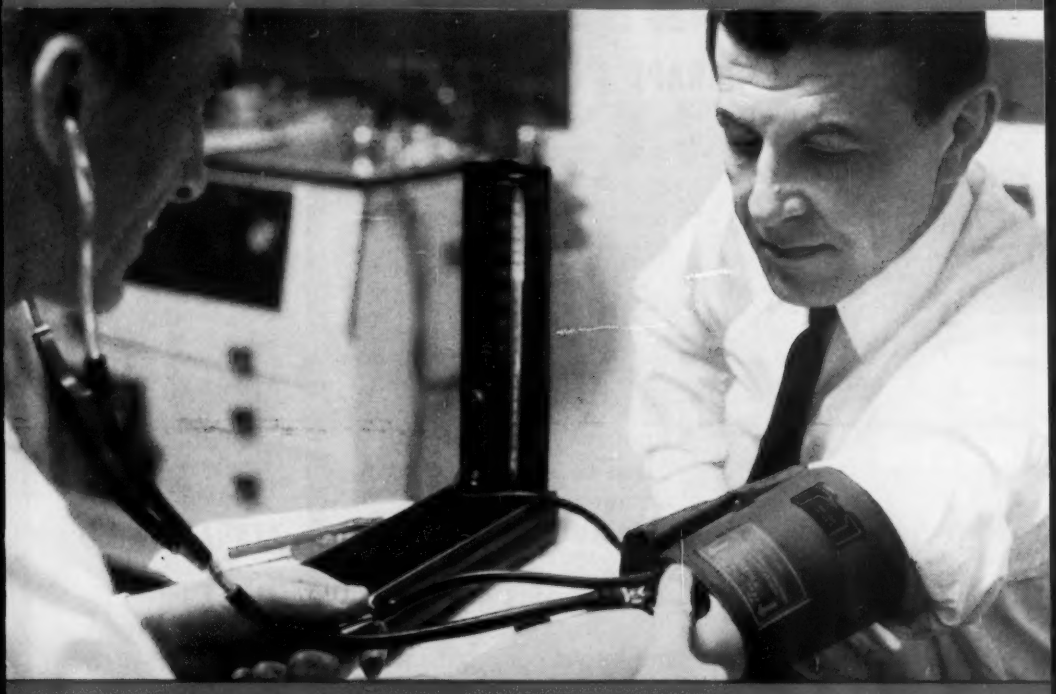
News and Comment

ANNOUNCEMENTS

Western Society for Clinical Research.—The Western Society for Clinical Research will hold its 12th annual meeting in Carmel-by-the-Sea, Calif., on Thursday afternoon, Friday morning, and Saturday morning, Jan. 29 through 31, 1959.

Information regarding the meeting may be obtained from the Secretary, William N. Valentine, M.D., University of California Medical Center, Los Angeles 24.

When anxiety and tension complicate HIGH BLOOD PRESSURE



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Literature and samples on request

1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc. **234**: 150, Aug. 1957.

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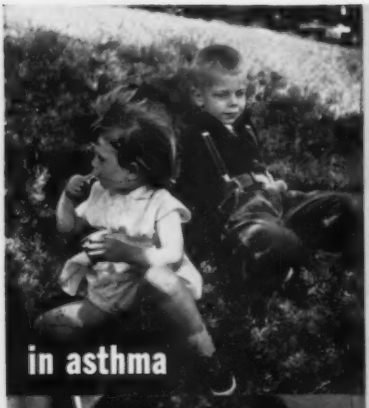

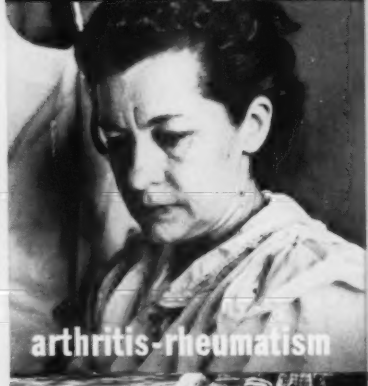

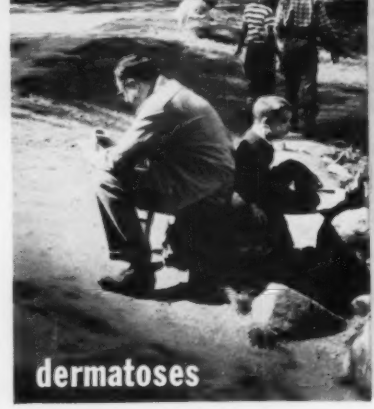

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1. Hutcheon, D. E., et al.: Paper presented at Am. Soc. Pharmacol. & Exper. Therap., Nov. 8-10, 1956, French Lick, Ind.
2. Johnston, T. G., and Cazort, A. G.: Clin. Rev. 1:17, 1958.
3. Warter, P. J.: J. M. Soc. New Jersey 54:7, 1957.
4. Individual Case Reports to Medical Dept., Pfizer Laboratories.
5. Strub. I. H.: To be published.

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Krane; Am. Pract. and Digest, 8: 1275, 1957

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Characteristics: New Cortrophin-Zinc provides corticotropin of unsurpassed purity with low foreign protein content. This reduces the risk of sensitization reactions.

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Pharmacology: A potent stimulator of cortical activity, Cortrophin-Zinc *does not depress* functioning of the suprarenal glands. Unlike the corticosteroids, adrenocorticotropic hormone arouses the adrenal glands to produce *natural* steroids in natural proportions. In a 5-year study of patients on ACTH therapy, no case of adrenal *or pituitary* depression or atrophy has been observed.

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Use of Cortrophin-Zinc with oral steroids is now recommended as a safety measure to supply the important suprarenal stimulation and lessen the hazard of atrophy. The periodic use of Cortrophin-Zinc is advocated with all steroid analogs, such as cortisone, hydrocortisone, prednisone, prednisolone, methylprednisone and triamcinolone.*

1. Banghart, H. E., *Bull. N. J. Acad. Med.*, 1:26, 1955.
2. Banghart, H. E., and R. K. D. Watanabe, *Am. Pract.*, 7:1957, 1956.
3. Davison, S., *N. Y. St. Jo. Med.*, *57*:3489, 1957.

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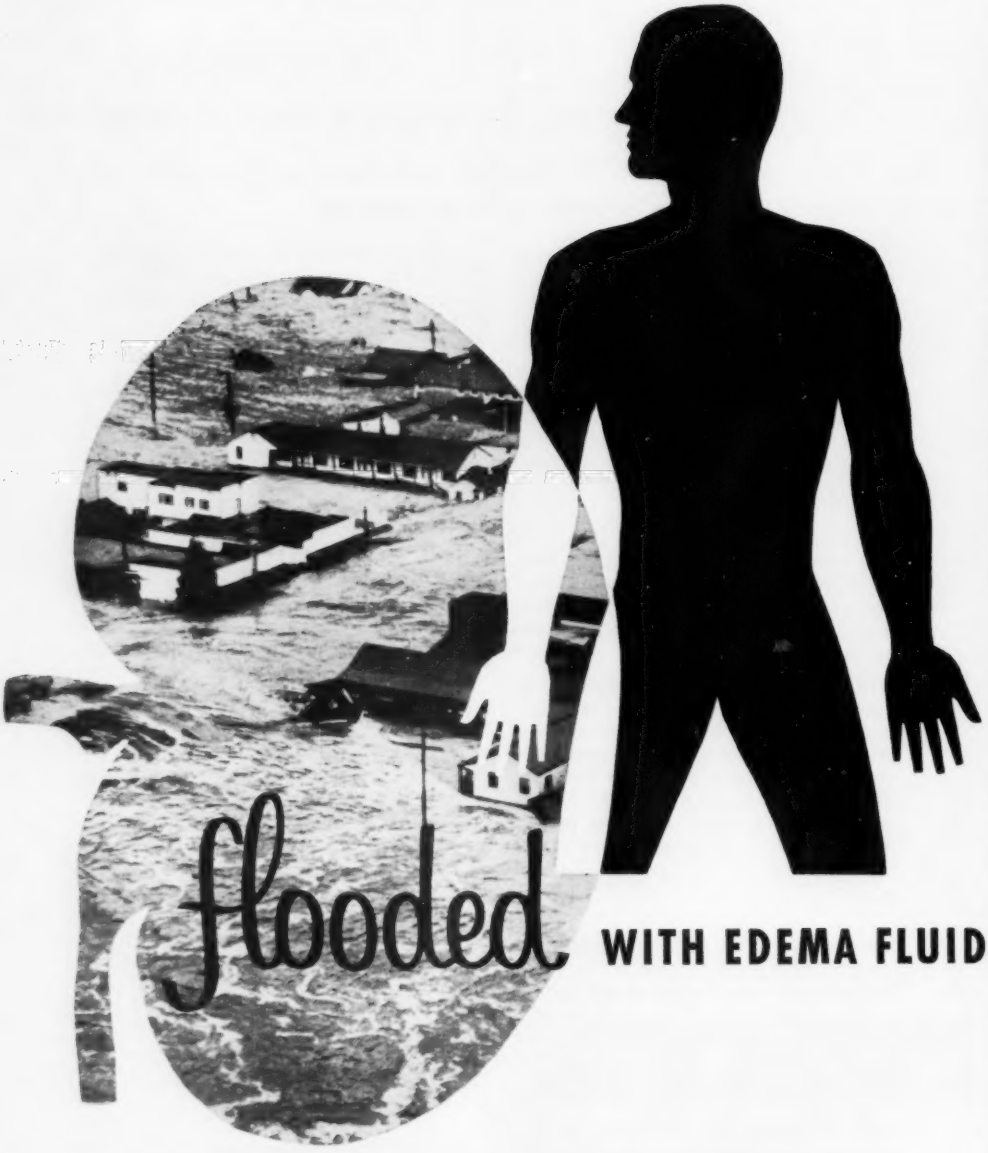

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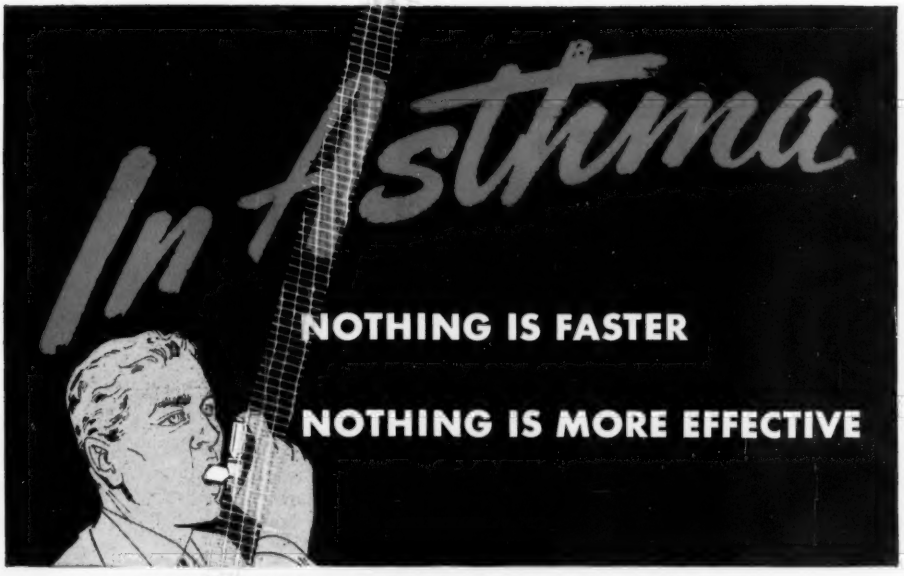

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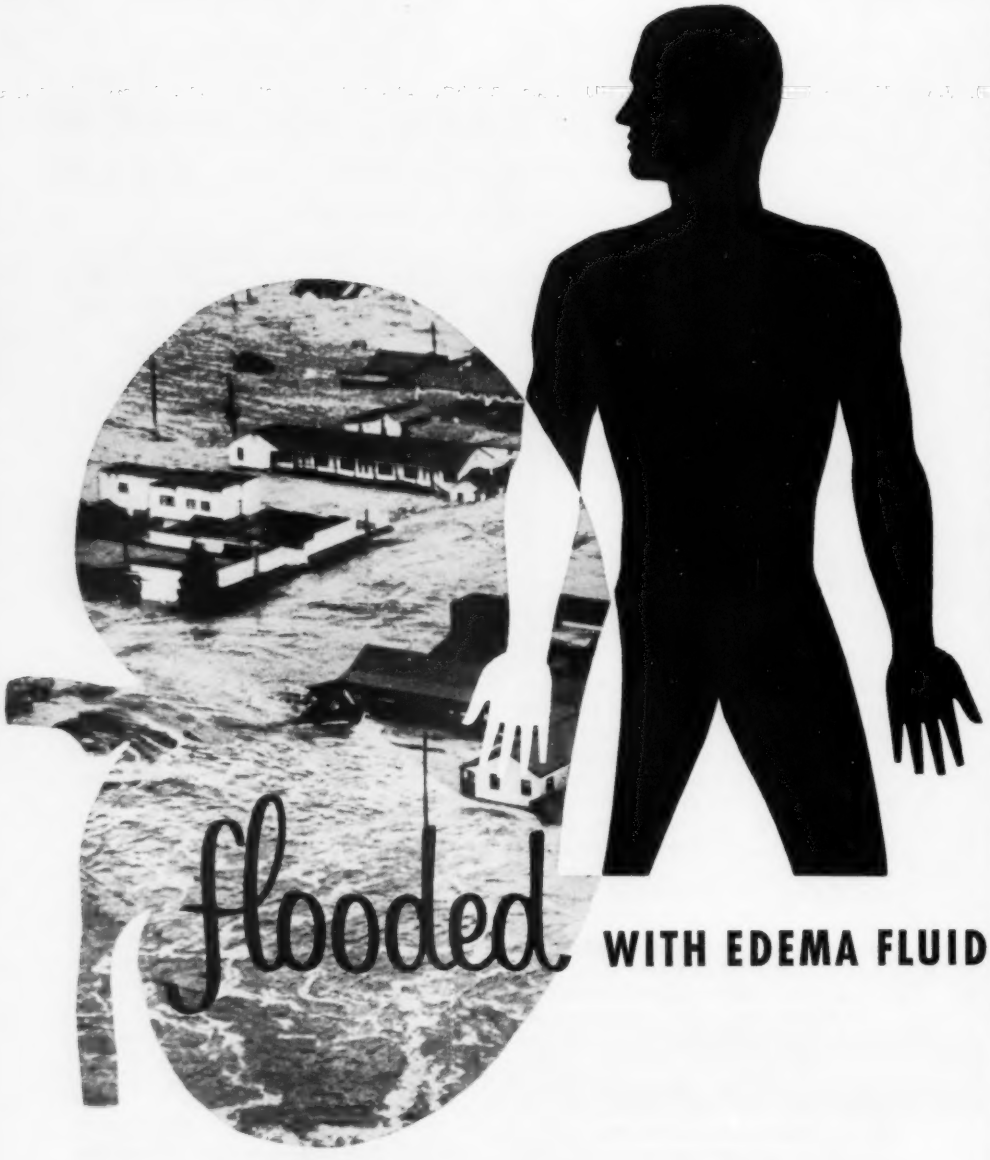

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